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MESTRADO EM ONCOLOGIA

ESPECIALIZAÇÃO EM ENFERMAGEM ONCOLÓGICA

# Central-line associated bloodstream infection rates and blood cultures collection assessment in Acute Leukemia patients: retrospective cohort study.

José Manuel Ferrer Martinez

M

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INSTITUTO DE CIÊNCIAS BIOMÉDICAS ABEL SALAZAR

M.ICBAS 2017

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# Central-line associated bloodstream infection rates and blood cultures collection assessment in Acute Leukemia patients: retrospective cohort study.

Dissertação de Candidatura ao grau de Mestre em Oncologia – Especialização Enfermagem Oncológica submetida ao Instituto de Ciências Biomédicas de Abel Salazar da Universidade do Porto.

Orientador – Professor Doutor Rui Manuel de Medeiros Melo e Silva

Categoria – Professor Associado Convidado com Agregação

Afiliação – Instituto de Ciências Biomédicas Abel Salazar da Universidade do Porto e Grupo de Oncologia Molecular e Patologia Viral do Instituto Português de Oncologia do Porto

Co-Orientadora – Professora Doutora Ana Espirito Santo

Categoria – Médico Assistente hospitalar na unidade de Oncohematologia do IPO Porto

Afiliação – Grupo de Oncologia Molecular e Patologia Viral do Instituto Português de Oncologia do Porto

## Agradecimentos

Dificilmente tenho palavras para expressar quão agradecido estou a muitas pessoas que estiveram junto de mim neste percurso. Muitos papéis foram conjugados ao longo desta etapa: pai, marido, profissional, estudante…e aquilo que podia parecer relativamente estruturado passou a ser um caos organizado, em que o dia a dia ganhou um novo significado.

Agradeço à Professora Doutora Berta Silva e à Professora Doutora Carmen Jerónimo pela oportunidade de ingressar neste mestrado e pela disponibilidade e atenção otorgada em todo o percurso.

Aos meus orientadores que tanto sofreram com a mihha teimosia: Professor Doutor Rui Medeiros, que me ensinou a contar uma história e a acreditar nas minhas ideias até ao fim; e à Professora Doutora Ana Espirito Santo, que me ensinou a por um ponto final nas frases e outorgou à palavra “paciência” um outro significado.

Aos meus colegas e amigos, Dr. Nelson e Dr. Sérgio, que fizeram o que provavelmente há de mais complicado na amizade….criticar construtivamente.

Às minhas colegas, Ariana, Ana Azevedo e Ana Felix que sempre me ajudaram neste trabalho, sem nunca perder a fé.

Ao Dr. Mariz, diretor da minha unidade, que em 2010 me deu a oportunidade de começar a investigar nesta área e que ainda hoje continua a acreditar que podemos mudar e melhorar muitas coisas.

Às minhas amigas e colegas de trabalho, que na fase final deste projeto trabalharam turnos seguidos para me ajudarem a terminar esta odisseia.

Ao Nuno, o meu companheiro de batalha nesta área. Juntos, tal como Asterix e Obelix, sempre defendemos as nossas ideias com toda a força, desde o nosso cantinho.

Ao meu cunhado Nando, que sempre me acompanhou mesmo estando longe…quantas saudades!

Aos meus sogros, que fizeram sempre o trabalho obscuro de amparar as quedas sem nunca eu dar por isso, obrigado!

Aos meus pequenos, Joel e Tiago. Ao Joel porque tantas vezes foi o meu companheiro de estudo e tantas vezes me ajudou a estudar. Ao Tiago, porque quanto mais obcecado eu ficava com isto mais ele me lembrava o que realmente era mais importante...nós.

Finalmente à Diana, a mulher extraordinária e forte da minha vida! Que este ano sofreu uma eternidade por minha causa. Porque se é difícil ajudar, muito mais difícil é querer e não poder. Nunca me faltou uma palavra de confiança e ânimo…ela sempre soube que chegaríamos lá, e eu…confiei cegamente nela. Obrigado!

Durante o desenvolvimento desta tese de mestrado foram realizadas:

- Candidatura para bolsa de investigação clínica com o projeto " *Needleless connector devices: Acute Leukemia patients, CLABSI and Mucosal Barrier Injury Microorganisms insight".* **Aceite** pelo Centro de Investigação do Instituto Português de Oncologia do Porto (CI-IPOP) com financiamento no valor de 8500 euros.

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# Abreviations

| | |
|---|---|
| AL: | Acute Leukemia |
| CVC: | Central Venous Catheter |
| CLABSI: | Central-line Associated Bloodstream Infection |
| CRBSI: | Catheter-related Bloodstream Infection |
| BSI: | Bloodstream Infection |
| ANC: | Absolute Neutrophil Count |
| BC: | Blood Culture |
| HAST: | Healthcare and Technology Synergy framework |
| CT: | Chemotherapy Treatment |
| MBIm: | Mucosal Barrier Injury Microorganism |
| DTP: | Differential Time to Positivity |
| MVC-PP: | Mechanical valve positive pressure |
| SSNC: | Split septum needleless connectors |

## Abstract

Background: Patients with acute leukemia (AL) have a higher risk of neutropenia. Central venous catheters (CVC) are indispensable devices during chemotherapy treatments and aplasia support.

Purpose: This clinical research aims to improve central-line associated bloodstream infection (CLABSI) assessment related to neutropenia and CVC manipulations using evidence-based science.

Methods: This is a single-center, retrospective cohort study reporting 28 patients diagnosed with AL, among 154 hospital admission episodes using a Hickman CVC for more than 72hour, undergoing chemotherapy treatment or in aplasia support from January 2013 to December 2015, at the Haematology Department of Portuguese Institute of Oncology (Porto).

Results: Forty-two Hickman catheters concerning 2130 hospital admission days (2007 catheter days) and overall 3032 CVC manipulations were reported. CLABSI was always reported in neutropenia admissions within cases presenting a median number of CVC manipulations superior to 15. Induction revealed superior duration of neutropenia (median 19, range 38 to 1) than aplasia support (median 12, range 23 to 3) [p=0.000]. Considering cumulative neutropenia-days prior to CLABSI, no statistical significance was found between induction (median 6.5, range 13 to 2) and aplasia support (median 4, range 9 to 1) [p=0.285]. No CLABSI risk between admissions undergoing neutropenia (induction and aplasia support) was found (RR 0.736, 95% CI, 0.311–1.745). Overall 6.47 CLABSI rate was reported, including 0.63 mucosal barrier injury microorganism ratio.

Conclusion: We concluded that in neutropenic patients, undergoing induction therapy or in aplasia support, CLABSI risk increases along with cumulative neutropenia days prior CLABSI and CVC manipulations. The MBIm ratio should be included to CLABSI rates assessment in AL patients. The specific characteristics of the patient, the product and the clinical practice (HAST framework) should be considered to promote the effectiveness of CVC clinical research.



**Key Words:** CLABSI; Acute Leukemia; Mucosal Barrier Injury Microorganism; Central Venous Catheter; Neutropenia

## Resumo

Introdução: Os doentes com Leucemia Aguda (LA) têm um grande risco de neutropenia. Os Cateteres Venosos Centrais (CVC) são instrumentos indispensáveis durante os tratamentos de quimioterapia e aplasia.

Objetivo: Com este trabalho de investigação pretende-se a avaliação das bacteriémias associadas ao CVC (CLABSI) , tendo em conta a neutropenia e as manipulações do CVC, tendo por base a prática baseada na evidência.

Métodos: Este é um estudo de coorte retrospectivo unicêntrico, incluindo 28 doentes diagnosticados com LA, entre 154 internamentos, usando CVC-Hickman por mais de 72h. Estes foram submetidos a tratamento de quimioterapia ou encontravam-se em aplasia desde janeiro de 2013 a dezembro de 2015, na Unidade de Hematologia do Instituto Português de Oncologia do Porto.

Resultados: Foram estudados 42 cateteres Hickman referentes a 2130 dias de internamento (2007 dias de cateter), num total de 3032 manipulações de CVC. A identificaçao da CLABSI ocorreu sempre em internamentos com neutropenia e com uma mediana de manipulações superior a 15. Durante o período de indução verificou-se uma duração superior da neutropenia (mediana 19, intervalo 38 a 1), do que durante o período de suporte de aplasia (mediana 12, intervalo 23 a 3) [p=0,000]. Considerando os dias cumulativos de neutropenia prévios a CLABSI, não foi encontrada diferença estatisticamente significativa entre indução (mediana 6.5, intervalo 13 a 2) e suporte de aplasia (mediana 4, intervalo 9 a 1) [p=0,285]. Não houve diferenças estatisticamente significativas de risco de CLABSI entre internamentos em neutropenia (indução e aplasia) (RR 0.736, IC 95%, 0.311-1.745). Foi reportada uma taxa de CLABSI de 6,47, incluindo uma razão de 0,63 de microorganismos de barreira da mucosa.

Conclusão: Nos doentes neutropénicos, submetidos a tratamento de indução ou em suporte de aplasia, o risco de CLABSI aumenta juntamente com os dias prévios de neutropenia, e com o número de manipulações do CVC. A razão de MBIm deveria ser incluida na avaliação das taxas CLABSI. Sendo que, o doente, o produto e a prática devem ser considerados como variáveis efetivas na investigação clínica associada a CVCs.



**Palavras-chave:** CLABSI; Leucemia aguda; Microorganismo de barreira da mucosa; Cateter Venoso Central; Neutropenia.

# 1. Introduction

## 1.1 Neutropenia and bloodstream infections in AL patients

Infectious diseases are important causes in both morbidity and mortality in hematology oncology patients. Patients with Acute Leukemia (AL), have a higher risk of neutropenia due to high-dose chemotherapy treatments (CT) and to malignancy itself. [1-3] Multiple chemotherapy cycles, antibiotic resistant bacteria and high transfusion rates are known predisposing factors that increase the incidence and prevalence of bloodstream infections (BSI). [4-6]

The AL is considered a group of neoplasms characterized by the transformation, undifferentation and clonal expansion of hematopoietic stem cells in the peripheral blood, bone marrow, and/or other tissues. [7] The classification of AL was previously based only on morfologhy (French-American-British [FAB] classification) and immunophenotype (acute myeloid leukemia [AML] or acute lymphoblastic leukemia [ALL]); now also relies on cytogenetic findings. Furthermore AL can also be stratified as de novo if acute leukemia arises without previous neoplastic treatment or secundary AL if the patient had a previous antineoplastic treatment. [8]

Different AL subtypes led to different therapeutic approaches and different outcomes. AML is associated with high dose chemotherapy treatments in induction, that includes both cytarabine and anthracyclines (i.e, 7+3 and/or SWOG regimens), and consolidation. Adult patients with ALL are also treated with aggressive and intense chemotherapy regimens, using multiple chemotherapy drugs in association. [7]

At diagnosis and during induction a functional neutropenia, i.e. a neutrophil dysfunction originated by bone marrow failure, can be identified. In this phase there is a higher infection risk. Also the administration of myelossupresived chemothearapeutic agents with therapeutic intent, such methotrexate, cytarabine, cyclophosphamide, doxorubicin or etoposide can lead to neutropenia. [9] The National Comprehensive Cancer Network (NCCN) considered neutropenia as the absolut neutrophil count (ANC) less than 500/µL or ANC less than 1000/mcL and predicted decline to 500/mcL or less over the next 48 hours. [10] The rate of decline of the ANC and the duration of neutropenia are considered as major factors to determine the infection risk. The evaluation of collateral therapeutics as corticosteroids (especially linked to CT admissions) or granulocyte colony stimulating grow factors can impair neutrophil function and delay neutrophil recovery, [11-12] leading to the hiding of clinical signs and symptoms in the infection episodes. [10]

When a clinical infection episode is reported, blood cultures (BCs) should be obtained. Fever (temperature ≥ 38.3ºC or temperature ≥ 38ºC persisting for more than one hour) is considered the most important nonspecific sign of infection in neutropenic patients. [10,13] BCs indication includes the presence of fever or, in their absence, the presence of other signs or symptoms of infection (chills or hypotension). [10] In the management of BCs, in neutropenic patients with fever, the number of sets obtained through the catheter and peripheral vein needed is not consensual. [13] However, the approach of obtaining BCs from the central catheter lines and a peripheral vein to determine the source of BSI based on the differential time to positivity (DTP) is considered an important procedure. [13-15] In a first infection event, large spectrum antibiotherapy is started as the Guidelines for Intravascular Catheter-related Infection of Infectious Diseases Society of America (IDSA) recommends, including gram-negative bacteria infections in neutropenic patients. [16]

In neutropenic patients, the natural host defense against local flora is reduced. AL patients undergoing CT can experience several complications, such as oral and gastrointestinal mucositis. [10, 17-18] Direct invasion across the colonic mucosa, due to the epithelial cell loss, can predispose patients to BSI. [18] Considering the National Healthcare Safety Network (NHSN) mucosal barrier injury microorganisms (MBIm) classification (2017) [19-20] and NCCN disruption of mucosal barriers insight [10], the viridians group *Streptococci, Enterococci spp., E. coli, Klebsiella* and *Enterobacter spp* are considered the most representative species associated with alimentary, sinopulmonary and genitourinary infection tracks. [10,19-20]

Several studies have identified the biofilm formation by individual multi-resistant pathogens as the major source of CVC infection. [21] The biofilm can be defined as communities of microorganisms attached to a surface. [22] The bacteria can initiate biofilm formation in response to a specific environmental impulse, such temperature, osmolarity, pH, iron, oxygen and nutrition. [22]

The pathogenesis of CVC infections includes two major routes: extraluminal (associated to short-term cvcs) and intraluminal (associated with long-term CVC). The colonization of the intraluminal route from the catheter tubing connection, catheter hub or IV fluids, are considered the most important infection threats. [23] Coagulase-negative *Staphylococcus* (CoNS), *Staphylococcus aureus, Pseudomonas aeruginosa and Enteric* gram negatives are considered the most common microorganisms involved in central-line devices infections, being the *Staphylococcus spp* considered the most representative. [24]

## 1.2 Central Venous Catheters

In 1929 Werner Forssmann discovered a new safety method in animals to introduce cardio-active drugs inserting a long urinary catheter via the antecubital fossa to the heart. He was awarded in 1956 with the Nobel Prize [25]; this was considered the first step in the journey of the central venous catheters (CVC). With the fastest-growing of the treatments, a new kind of long-term catheters were needed due to the different type of treatment modalities that allowed the administration of intravenous therapy, transfusion support and blood sampling [26]

There are four major catheter types based on their designs: Non-tunnelled CVCs, Tunnelled CVCs (i.e, Hickman or Broviac catheters), Implantable ports and peripherally inserted central catheter (PICC). [27] The placement and type of CVC depends on the preferences of the patient, the healthcare provider and the IV therapy duration. [28] The principal way for healthcare professionals to reduce and control the pathogenesis of infections in central line devices are the insertion and maintenance procedures. [23] Several studies report behavioral changes, education of healthcare professionals, insufficiently trained nurses, a low nurse-to-patient ratio and protected environments directly related to infection control strategies. [29-31]

Healthcare and Technology Synergy (HAST) framework considered that the patient, the product and practice are the central elements related with effectiveness of clinical research associated to CVC. [32] Insertion CVC procedure was largely studied and compared with the maintenance of CVC procedure. [33] The real value of CVC management still remains unclear due to the low description and few management detailed reports in clinical research. [29-33]

Catheter-related occlusion due to mechanical obstructions and catheter-related infection are the most important complications in the management of the central venous devices. [5, 34] In AL inpatients the risk of these complications is high due to myelossupresion, specially neutropenia and thrombocytopenia. [35-36] The most common modifiable risk factors known to increase overall catheter-related bloodstream infection (CRBSI) are CVC-life [14], parenteral nutrition [37], multi-lumen CVC [38], high workload [39] or CVC-associated thrombosis [34], being the imunocompromised status the highlighted non-modifiable risk factor in hematology oncology patients. [2,40]

Large osmolarity spectrum drugs, several infusion and perfusion volumes and lower thromboses rates lead Hickman catheters to be suggestted as the best vascular access devices option in AL patients undergoing high dose CT since 80´s decade. [28] Ming Y.

Ling et al., 2013, developed at Mayo Clinic Rochester a clinical research comparing the efficacy of 84 Hickman Catheters versus 64 PICCs in the treatment of AML patients. The study reported no significant differences in catheter-related thrombosis, central-line associated bloodstream infections (CLABSI) and CRBSI rates. However, catheter-related occlusion was significant higher in PICCs (20.43 versus 1.25 per 1000 CVC-days, p=.0001). [28]

Tunneled catheters report lower infection risk than non-tunneled catheters. [40] Mollee, et al., 2011, determined the incidence and risk factors for CABSI (CLABSI definition according to the Australian Infection Control Association) of all patients requiring a central venous access device (CVAD) in a hematology-oncology department. They considered the CVAD type, patient diagnosis, side of insertion and the number of prior-line insertions as risk factors of CABSI. The study suggests that the superior CABSI risk in right-sided lines (HR: 1.60; p=0.027) when a higher number of previous lines were inserted (HR: 1.2; 95% CI: 1.03-1.41). Considering hematological malignancies group (acute leukemia, myelodisplastic syndrome, non-Hodgkin Lymphoma and multiple myeloma), superior CABSI risk was reported (HR: 3.17; 95% CI: 1.63-6.16). When CVAD type (tunneled lines versus PICCs) and aggressive hematological malignancies group (AL and myelodisplastic syndrome) were associated with the analysis, no significant CABSI risk was found (HR 1.43; p=0.12) between them. Study results revealed that progressive use of CVC-lumens didn't increase the infection risk. However the infection is earlier reported in CVCs with more lumens (3 versus 2). In the case of Exit-site and Tunnel infections, hematological recovery was required for infection resolution. [41]

### 1.2.1 Management of CVC: insertion and maintenance

As recommended CVC insertion procedure takes place in a operating room to reduce the infection risk. CVC-placement (jugular or subclavian) and CVC-life are considered infection risk factors. [29] Glaucia Martinho, et al., 2013,developed a clinical research in 56 patients undergoing HTSC (Hematological Transplantation Stem Cell) reporting significant differences between the jugular (ID: 31.7 per 1000 CVC-days) and subclavian (ID: 4.2 per 1000 CVC-days) CVC-placement (HR, 0.21 ;95% CI: 0.62-0.74, p=.02). [42] Walter Zing and Didier Pittet, members of the Infection Control Program and WHO Collaborating Centre on Patient Safety (Geneva), suggests in a comment of The Lancet (2016) that studies published between 2014 to 2016 report that subclavian access site is better than the jugular. [43]

Eitan Kugler, et al.2015, compared CVC-placement time <7 days versus ≥ 7days in a prospective surveillance study in patients with AL. The study suggests an association between late CVC-placement time and CLABSI (OR 3.4, 95% CI 1.1-10-45, p=.03). [36] Parienti,et al. 2015, published a systematic review entitled "*Intravascular complications of central venous catheterization related to CVC-placement*" in the New England Journal of Medicine. The study suggests that a jugular insertion site and that CVC-placement time can be considered extrinsic risks of CLABSI, and both can be modified. [44]

The clinical research related to CVC maintenance procedures in AL patients is scarce. [29-30] Guidelines for the prevention of Intravascular Catheter-Related infections published by the Control Disease Center (CDC) in 2011 are based on education and training of CVC procedures. [31] There is a lack of clinical research, concerning CVC management details with different methodology between studies that can improve and sustain the development of Guidelines. Only 45.5% of the major recommendations are considered category IA (strongly recommended for implementation and strongly supported by well-designed experimental, clinical, or epidemiologic studies). Considering the administration sets replacement and needleless intravascular catheter systems, 46.14% of the recommendations are classified as Unsolved Issue and/or category II (suggested for implementation and supported by suggestive clinical or epidemiologic studies or a theoretical rationale). [31] The implementation of multifaceted strategies (bundled) to prevent intravascular catheter-related infections is based on recommended practices, category IB (strongly recommended for implementation and supported by some experimental, clinical, or epidemiologic studies and a strong theoretical rationale; or an accepted practice supported by limited evidence) or superior. [31]

The National Evidence-Based Guidelines for Preventing Healthcare-Associated Infections in NHS Hospitals in England (epic) and CDC guidelines reported, similar recommendations for catheter management. [45] In 2013, last update (epic 3), the 27.27% of the recommendations were based on the high level consistency of results (Class A). However, 63.63% of the recommendations were considered Class D/GPP (low level evidence related to non-analytic studies, expert opinion, legislation and good practice points). [45]

In the case of AL patients, the literature reports a medley of clinical research related to CVC procedures [29], and it is possible to find two departments following the same guideline recommendations and reporting different protocols (e.g., mechanical valve needleless connectors or split septum connectors, heparin or sodium chloride to CVC lock). [31,33]

## 1.3 Central-line associated and related bloodstream infections

Actually, CLABSI is considered the most costly health-care-associated infection. Annually 200.000 to 400.000 episodes of CLABSI related to long-term catheters are identified in the USA. [29] The NHSN considered CLABSI *"as a primary bloodstream infection that develops in a patient with a central line in place within 48-hour period before onset of the bloodstream infection that is not related to an infection at another site".*[46]

The CDC has established 5 catheter-associated infection definitions: Localized catheter colonization, Exit-site infection, Clinical exit-site infection, Infusate-related bloodstream infection, and Catheter-related bloodstream infection (Table I). [31, 40]

**Table I. CDC catheter-associated infection definitions**

| | |
|---|---|
| Localized catheter colonization | Microorganism growth (>15 CFU) from catheter tip, subcutaneous segment or catheter hub |
| Exit-site infection | Erythema or induration (≤2 cm) of the catheter exit site, in absence of BSI or concomitant purulence |
| Clinical exit-site infection (tunnel infection) | Exit-site infection (≥2cm) of the catheter exit site, in absence of concomitant BSI |
| Infusate-related bloodstream infection | Infusate and blood cultures reportthe same microorganism with no other identifiable source of infection |
| Catheter-related bloodstream infection | One positive blood culture obtained for peripheral vein and significant catheter segment microorganism growth identified by DTP, 3:1 ratio, or semiquantitative/ quantitative cultures in central-lines (same microorganism reported) |

CLABSI and CRBSI are usually reported as incidence density (ID) (surveillance studies) or as a proportion (pathogen colonization studies). [31] The ID reports the number of bloodstream infections per 1000 catheter-days or patient-days, being the catheter-days the best choice for analysis. [31] CLABSI is considered the classic concept in surveillance programs, being CRBSI the most used definition, regarding diagnosis and treatment purposes. [29]

Recently, a new MBIm insight was added leading to a hard assessment of management CVC procedures, especially in hematology-oncology departments, where the infection due to MBIm is common. [19, 47-48] Modified CLABSI definitions related to disruption of

mucosal barriers can reduce the number of CLABSI reported. However, CVC management could still be the source of CLABSI associated to MBIm. [29] Arne Simon, et al., 2016, suggests, in a European systematic review of surveillance of BSI in pediatric centers, that pay for performance is an important reason for changing the surveillance definitions in U.S.A. [49]

Zakhourand, et al., 2016, published in *Lancet Infectious Diseases* a review of the Catheter-related infections in patients with hematological malignancies. They present an incidence of 14.4 CLABSI rate per 1000 catheter days in AL patients (adjusting CLABSI rates to MBIm events, this value decreases to 8.2). [29] These clinical results are based on Digiorgio, et al., 2012, clinical research. They developed a modified surveillance definition of CLABSI, mCLABSI, considering microbiology disruption of mucosal barriers. The study reports 22-bed bone marrow transplant (BMT) and acute leukemia units. Considering the new concept, CLABSI rates decrease to 2.0 per 1.000 CVC-days regarding 6.0 per 1000 CVC-days in BMT units. This new concept, mCLABSI, is associated with an increase of Coagulase-negative staphylococci (CoNS) rates regarding enteric pathogens. [50] In 2013, Joshua Lukenbill, et al., suggested in a retrospective study of AML and Myelodisplastic syndrome patients undergoing stem cell transplantation, a new MCLABSI definition. The study considered OCLABSI as CLABSI original definition and it is compared with the new concept. The MCLABSI excludes *Viridians* group *Streptococci* species in patients with mucositis, *Enterococcus, Enterobacteriaceae*, or *Candida* species. [35] Finally, study results suggested a lower prevalence of MCLABSI than OCLABSI, as previous Digiorgio clinical research. [50]

## 1.4 Catheter-related occlusion and thrombosis: Needleless connectors and Solution-lock

Catheter-related occlusion can be observed considering two different sources: Nonthrombotic and Trombotic causes. [34] The cloth is considered the most common cause of occlusion, however, other causes such catheter pinch-off, precipitation of drugs solutions and catheter migration can produce the inability to aspirate blood. [40] Occlusion (partial and complete) should be considered when the capacity to blood withdrawal is compromised and the ability to flush fluids is lost. The infuse ability is an especial condition related to partial occlusion instead of complete occlusion. [34, 40]

Thrombosis formation can be related to CVC-placements (superior vena cava or upper extremity veins) and its characteristics (CVC-lumen). NapalKov, et al., 2013, presented a study where CVC-related thrombi formation was observed within 30 days of initial CVC-

placement in patients with CVC or hemodialysis catheters. [51] Considering the thromboses and infection dichotomy, clinical thrombosis manifestations could increase CVC-related infection risk. [52]

The use of thromboembolitic agents by syringe or stopcock method declothing using streptokinase, urokinase and alteplase is recommended. [34]

- ✓ Needleless Connectors: Split septum needleless connectors and Mechanical valve positive pressure

Needleless connectors are devices used to create a safety door catheter access. [31] The split septum needleless connectors (SSNC) are considered the first generation of these devices, followed by the mechanical valve positive pressure (MVC-PP) adaptation. The MVC-PP was developed to reduce catheter-related occlusion rates. [26, 34, 53] Both devices can be used with sodium chloride or heparin. If flushing-pause and positive-pressure CVC-lock techniques are not performed, the SSNC can increase the risk of occlusion and thrombosis due to tip blood reflux, observed when the syringe or cannula is removed. [54-55] The MVC-PP can reduce catheter-related occlusion rates using a mechanical valve inside the connector that does not allow the reflux of blood, decreasing the probability of small thrombi formation. However, the SSNC reports low infection rates than MVC-PP in the literature. [26, 31]

- ✓ Heparin and 0.9% sodium chloride

The CVC management related to the CVC-lock solution used (heparin or normal saline 0.9%) still remains controversial and prospective trials are needed. [56] The duration of heparin lock, the concentration of heparin solution, heparin induced trombocytopenia or coagulophats are limitations for the use of this solution. [56] However, the fact that heparin has a shorter half-life and not a thrombolityc capacity, and that it promotes a natural prevention of cloth progression lead to suggest that heparin is a good solution to CVC-lock. [57]

Theoretical rationale studies support that using heparin to CVC-lock can reduce catheter-related thrombosis and fibrin deposition (formation film). Bradford, et al., 2016, in their systematic review "*Heparin versus 0.9% sodium chloride intermittent flushing for the prevention of occlusion in long term central venous catheters in infants and children*" published in "*The International Journal of Nursing Studies",* report that most of institutions recommend the use of heparin when CVC is not in use. The study reports that clinical research is associated with a quality study ranged from low to very low evidence. Indeed,

different protocols with several concentrations and frequencies of heparin were related. Finally, this study concludes that more well-designed researches are required. [58]

Alberto Dal Molin, et al., 2015, suggested that normal saline flushing in totally implanted venous access devices is not inferior to heparin flushing (with a study power lower than 56%). In the case of occlusion types, study results revealed a partial occlusion more frequent than complete, being only one complete occlusion observed in the saline group. The study did not include AL patients and did not consider neutropenia condition. The authors present the linical study of Cesaro, et al., 2009, where 203 pediatric patients were randomized in a trial that revealed an increased-rate of complications in patients using Broviac-Hickman catheters flushing with normal saline solution. [59]

Healthcare professionals avoid heparin due to the heparin-induced thrombocytopenia [31]; however in the particular case of AL patients, thrombocytopenia is considered a frequent condition. [40] Abdelkefi, et al. 2007, studied 246 patients with non-tunneled central venous catheters comparing the use of continuous infusions of heparin and low-dose unfractionated heparin to prevent CRBSI. The study did not reported heparin-induce thrombocytopenia and severe bleeding complications between groups (p=1.00). [60]

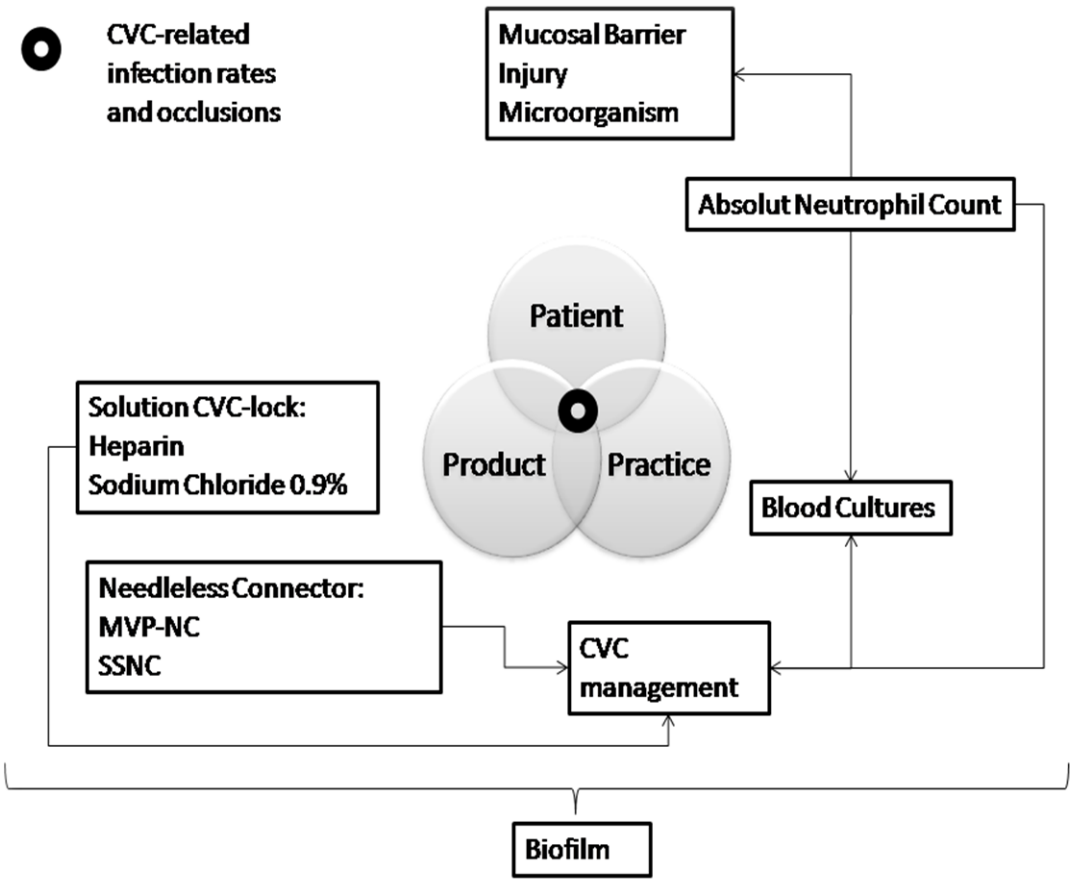
Considering Guidelines perspective, the CDC (category II) and EPIC3 (Class D/GPP) guidelines do not recommend routinely use of anticoagulants to prevent CRBSI. [31, 45] In fact, the use of normal saline to CVC-lock, that are accessed frequently, is considered a Class A recommendation by EPIC3 guidelines. However, when the catheter is accessed infrequently several doubts still remain, despite that, low infection rates outcomes reports were found. [45]

## 2. Hypothesis Test

The null hypothesis ($H_0$) considered: CLABSI assessment of AL patients undergoing induction, chemotherapy treatment or aplasia support phases using Hickman catheters is not associated [alternative hypothesis ($H_1$), are associated] to ANC and CVC manipulations at the hematology department of the Portuguese Institute of Oncology, Porto.

CVC manipulations and ANC are considered the exposure or event of interest. CLABSI and non-CLABSI related with the BCs assessment are considered as the outcome of interest.

### 2.1 Organigram



## 3. Objectives

Primary

CLABSI rates assessment in AL patients using a Hickman catheter undergoing chemotherapy treatment, or aplasia support phases considering ANC and CVC manipulations;

Specific

To evaluate:

- ✓ ANC and CLABSI
  Duration of neutropenia and cumulative prior CLABSI day assessment;
  CLABSI reported considering ANC related;
  Neutropenia Ratio assessment;

- ✓ Blood Cultures Collection
  Blood culture assessment related to the episodes, microbiology and infection source.
  Transfusion support related to the blood culture collection;

- ✓ Catheter-related occlusion
  Catheter-related partial or complete occlusion associated with infection risk;
  Platelet count, Transfusion support and CVC-life associated with catheter-related occlusion;

- ✓ Mucosal Barrier Microorganism
  Microorganism recovery assessment considering the mucosal barrier injury related;
  Mucosal barrier injury microorganism Ratio assessment and CLABSI;

# 4. Material and Methods

## 4.1 Selection and description of participants

A single-center, retrospective cohort study was performed, including all consecutive AL patients using a Hickman CVC for more than 72h, undergoing chemotherapy treatment or aplasia support from January 2013 to December 2015, at the Haematology Department of the Portuguese Institute of Oncology (Porto).

Patients older than 18 years old with newly diagnosed or relapsed AL admitted for chemotherapy treatment (CT) or aplasia support and with a CVC inserted during the study period were included. Patients in supportive care, who had previous hematopoietic stem cell transplantation, with clinical septicemia at the moment of the CVC introduction, with insertion procedure complications or with acute promyelocytic leukemia diagnosis were excluded.

The number of hematology-oncology patients with long-term catheter inserted since 2013 to 2015 were 123, being 32 diagnose by acute leukemia (statistics hospital information, 8$^{th}$, March 2016). Using the Raosoft® sample size calculator [61] with a 5% margin of error, 95% confidence level and 50% response distribution parameters, minimum of 27 inpatients was recommended in the research. After inclusion and exclusion criteria (septicemia n=3, insertion procedure complication n=1), 28 AL patients with a Hickman catheter were included.

## 4.2 Data collection

Data concerning each patient's background was daily collected from the medical records since CVC placement day. The daily data assessment ended when the CVC was removed from sepsis or in the end of treatment. When the final eligible patient was admitted to the study a minimum of one-month follow up was considered. The baseline demographic data were collected on the day of CVC placement and the assessment was encompassed in every hospital admission.

## 4.3 Neutropenia and Central-line infections definitions

Neutropenia [10] was considered when ANC (Absolute Neutrophil Count) ≤500 cells /µL, or when no differential count was available and WBC (White Blood Count) ≤1600 cells/µL

was reported (previous statistical correlation analysis). The total of continuous neutropenia-days was considered as the duration of neutropenia. Overall neutropenia-days related to catheter-days was considered Neutropenia Ratio (NR). Neutropenia days-prior CLABSI was considered the number of neutropenia-days since the first neutropenia-day to CLABSI reported.

CLABSI and CRBSI rates were calculated considering BCs yielding an organism (positive culture in peripheral vein and at least one CVC-line) per 1000 CVC-days. CLABSI was considered in patients with a central line in place within 48-hour period and bloodstream infection that is not related to an infection at another site. [10,31] When DTP was reported positive, CRBSI was considered. The ratio between the MBIm and the total of microorganism recovered was considered MBIm ratio.

### 4.4 CVC manipulations and Catheter-related occlusions definitions

Manipulation was considered in every approach to CVC with at least one open line. One manipulation of the CVC was considered every time that the CVC line was opened to change the administration sets, collect blood samples or blood cultures (BCs). When transfusion support was performed two manipulations were considered.

The occlusion was considered when the capacity to blood withdrawal was compromised and the ability to flush fluids was lost. Partial occlusion (inability to aspirate blood, but ability to infuse through the catheter) and complete occlusion (inability to aspirate blood and infuse through the catheter) were reported. Catheter-related occlusion was calculated considering the occlusion events per 1000 CVC-days. [34] Catheter Lock was considered when the solution was injected into the catheter lumen dead space until it was filled to be accessed again. [27]

### 4.5 Technical department information

The department consisted of 20 beds distributed among eight double and four single rooms, all equipped with positive pressure ventilation and HEPPA filters. AL, non-Hodgkin/Hodking Lymphoma and Multiple Myeloma patients were admitted in the department. The insertion of CVCs was performed by medical staff in an operating room [29] located in the department, and daily management of CVCs was performed by nursing staff. The ratio nurse/patient ranges between 1:4 and 1:8, being the principal CVC maintenance procedures performed in the morning shift when the ratio is higher. During

the study period, no other relevant departmental changes were implemented, including CVC insertion, CVC management procedures, indication for BCs, and BCs assessment.

### 4.6 Blood culture collection and empirical antibiotic use policy

BCs collected by control indication, the ones non-department collected and hospital acquired infections [10, 16] were not included in the study. For every episode with an indication for BCs, samples were collected first from a peripheral vein followed by the CVC line with no more than five minutes between samples (when samples from CVC lines become positive 120 minutes or more before peripheral vein samples, this is known as differential time to positivity). [62] BCs collection were performed by one single nurse. BC samples were collected with a minimum of 5 ml of blood, when possible, in BACTED PLUS Aerobic/F® vials [63] and were analyzed by the microbiology department. In an attempt to reduce false positive BC results, due to the positive needleless connector and negative hub contamination, needleless connectors were removed before collecting BC samples. Large spectrum antibiotherapy was started following the indications of the 2009 Infectious Diseases Society of America Guidelines for Intravascular Catheter-related Infection, that recommend to treat gram-negative bacterial infections in patients undergoing neutropenia or septicemia special conditions. [16]

### 4.7 Blood Cultures Assessment

All episodes of positive BCs were analyzed in all hospital admissions, and all negative BCs were counted to epidemiological research. The first BCs collection was considered as the first episode. If new BCs samples were collected and a second subsequent episode was considered and acted upon. In the first 72-hours after the previous episode, new first episode was considered when a new microorganism was isolated, when a change of the antibiogram, or a change the hub of the colonization in the central line occurred. All episodes over 72-hours, to the previous collection, were considered new first episode. [64-65]

The assessment of CRBSI, CLABSI, BSI or colonization was completed by the analysis of the microbiological results (Figure I) with a clinical specialist nurse and hematological medical specialist evaluation. [2,10,27,31]

**Figure I. Blood Culture results: BSI, CLABSI and CRBSI assessment**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Peripheral Vein** | **+** | **+** | **+** | **+** | **+** | **-** | **-** |
| **CVC-line 1.0 mm** | - | + | -/+ | + | -/+ | + | -/+ |
| **CVC-line 0.6 mm** | - | -/+ | + | -/+ | + | -/+ | + |
| **DTP** | N.A. | - | - | + | + | N.A | N.A |
| **Microbiological Analysis** | BSI | CLABSI | CLABSI | CRBSI | CRBSI | Colonization | Colonization |

(N.A: not applicable; +:positive; -:negative)

## 4.8 Product and practice management

The management of CVCs followed the CDC (2011) guideline recommendations. Hickman catheters (Vygon®) without any antimicrobials were inserted in the subclavian vein. All catheters were double lumen (CH/F 7, lumen no. 1=0.6mm, lumen no. 2=1.0mm). No antibiotic prophylaxis was performed. Specific technical information about CVC management included the use of: chlorhexidine 2% in alcohol 70% solution for needleless connector disinfection, split septum needleless connector (Bionecteur, Vygon®), and sodium heparin 20 IU/ml (Fibrilin®). Administration sets (not receiving blood, blood products or fat emulsions) and needleless connectors were changed in all the blood culture collections and no more often than 72-hours to reduce the infection risk associated with biofilm formation. [22,64]

## 4.9 Data analysis

Data analysis is conducted using IBM SPSS Statistics for Windows (SPSS Inc., Version 24.0) licensed by ICBAS-UP (Instituto de Ciências Biomédicas Abel Salazar - Universidade do Porto; Master Degree Oncology Program). A continuous variable was reported by median and range. Categorical variables were reported as frequency and percentages. Any association between two continuous quantitative variables were analyzed by Perason´s (r) correlation test. Normality tests (Kolmogorov-Smirnov) reported

a sample without normal distribution, considering that, hypothesis tests were analyzed by non-parametric test. Differences between categorical measures were performed using Mann Whitney U test, and Relative Risk was performed by confidence interval of 95%. A *p* value of ≤ 0.05 was determined to be statistically significant.

Protection of personal data

The study was approved by the Ethics Committee (CES IPO: 137/2016) (appendix II) of the Portuguese Institute of Oncology (Porto) on 16 June, 2016. All data were treated in compliance with the Portuguese Law nº 67/98 of 26 October concerning the protection of personal data.

## 5. Results

In this study 154 hospital admission episodes were analysed (Table II). Twenty eight patients diagnosed with AL [AML, n=17(67.7%); ALL, n=11(39.3%), p=0.345] were identified, 75% (n= 21) female and 25% (n= 7) male, with a median age of 49 years (range, 68 to 23).

**Table II. Baseline Hospital Admissions Characteristics**

| **Characteristic** | **AML** | **ALL** | **p** |
|---|---|---|---|
| Admissions, n(%) | 97(62.9) | 57(27.1) | 0.002 |
| Age, years, median (range) | 49 (68-25) | 53(66-23) | 0.750 |
| Gender Male, n(%) | 10(6.5) | 18(11.7) | 0.186 |
| Female, n(%) | 87(56.5) | 39(25.3) | 0.000 |
| Relapse Yes | 18(11.7) | 0(0) | 0.000 |
| No | 79(51.3) | 57(37) | 0.072 |
| Admission days(ID), n[median(range)] | 1470[12(42-5)] | 660[7(38-4)] | 0.001 |
| CVC days, n[median(range)] | 1394[12(38-5)] | 613[7(35-4)] | 0.000 |
| ANC ≤ 500 cells/μL n[median(range)] | 943[15 (38-2)] | 269[10(33-1)] | 0.002 |
| Neutropenia Ratio | 0.68 | 0.44 | NA |
| Number of CVC / patient, median(range) | 1(4-1) | 1(2-1) | 0.200 |
| CLABSI, n(%) | 9(69.2) | 4(30.8) | 0.852 |
| CRBSI (% of CLABSI*diagnose) | 0(0) | 1(25) | NA |

AML acute myeloid leukemia ;ALL acute lymphocytic leukemia; NA not applicable

Considering the distribution of hospital admission by gender associate to age, significant lower median age in male group was reported [male, median 43, range 66 to 23; female, median 49, range 68 to 25; p=0.046]. No CLABSI risk was found considering diagnose [RR 0.976, 95% CI, 0.887-1.074], relapse [RR 2.267, 95% CI, 0.688-7.472], age [≤50/>50 years, reference group by sample median age; RR 0.922, CI 95%, 0.325-2.618] and gender [RR 2.000, 95% CI, 0.663-6.034]. No CLABSI risk was found considering age, diagnosis and gender related (Table III).

Considering the age [≤50/>50 years] RR ratio reference=1, the relation of CLABSI risk related to age was reported (Table IV). No CLABSI was observed in patients younger than 25 or older than 60 years old.

**Table III. Age, diagnose and gender CLABSI risk related**

| | CLABSI | Non-CLABSI | RR CI 95% |
|---|---|---|---|
| **Age*Diagnose** | | | |
| AML | | | |
| ≤50 years(Ref) | 6(6.2) | 55(56.7) | 1.180 (0.314-4.433) |
| >50 years | 3(3.1) | 33(34) | |
| ALL | | | |
| ≤50 years(Ref) | 1(1.8) | 24(42.1) | 0.427 (0.047-3.858) |
| >50 years | 3(5.3) | 29(50.9) | |
| Gender*Diagnose | | | |
| AML | | | |
| Male | 1(1.1) | 9(9.3) | 1.088 (0.151-7.823) |
| Female | 8(8.2) | 79(81.4) | |
| ALL | | | |
| Male | 3(5.3) | 15(26.3) | 6.500 (0.725-58.674) |
| Female | 1(1.8) | 38(66.7) | |
| Gender*Age | | | |
| Male | | | |
| ≤50 years(Ref) | 2(7.1) | 14(50) | 0.750 (0.123-4.589) |
| >50 years | 2(7.1) | 10(35.7) | |
| Female | | | |
| ≤50 years(Ref) | 5(4) | 65(51.5) | 1.000 (0.282-3.550) |
| >50 years | 4(3.2) | 52(41.3) | |

**Table IV.CLABSI risk age related**

| Age | CLABSI | Non-CLABSI | RR CI 95% | RR ratio |
|---|---|---|---|---|
| ≤25 | 0(0) | 19(12.3) | - | - |
| >25 years | 13(8.4) | 122(91.6) | | |
| ≤30 | 1(0.6) | 26(16.9) | 0.392(0.053-2.888) | 0.43 |
| >30 years | 12(7.8) | 115(74.7) | | |
| ≤35 | 2(1.3) | 48(31.2) | 0.378 (0.087-1.642) | 0.41 |
| >35 years | 11(7.1) | 93(60.4) | | |
| ≤40 | 2(1.3) | 53(34.4) | 0.327 (0.075-1.424) | 0.35 |
| >40 years | 11(7.1) | 88(57.1) | | |
| ≤45 | 3(1.9) | 57(37) | 0.470 (0.135-1.639) | 0.51 |
| >45 years | 10(6.5) | 84(54.5) | | |
| ≤50 years | 7(4.5) | 79(51.3) | 0.922 (0.325-2.618) | 1 |
| >50 years | 6(3.9) | 62(40.3) | | |

| | | | | |
|---|---|---|---|---|
| ≤55 years | 10(6.5) | 92(59.7) | 1.699 (0.489- 5.909) | 1.84 |
| >55 years | 3(1.9) | 49(31.8) | | |
| ≤60 years | 13(8.4) | 112(73.4) | - | - |
| >60 years | 0(0) | 28(18.2) | | |
| ≤65 years | 13(8.4) | 125(81.2) | - | - |
| >65 years | 0(0) | 16(10.4) | | |

Reasons for hospital admission were induction treatment [32 (20.8%)], aplasia support [48 (31.2%)], CT [70 (45.4%)], and CT + aplasia [4 (2.6%)]. Induction and CT hospital admissions were summarized by AML and ALL CT protocols [7+3, 66 (42.9%); SWOG, 22 (14.3%); Consolidations, 7 (4.5%); BF12, 1 (0.6%); VC, 1 (0.6%)] and [hyper CVAD A[1], 31 (20.1%); hyper CVAD B[2], 17 (11%); All Rez BFM90, 3 (1.9%) and BFM90, 6 (3.9%)]. Considering CT protocols related to CLABSI, differences by AL groups were reported, AML [6 (46.2%) 7+3, 3 (23.1%) SWOG and ALL [(3 (23.1%) hyper CVAD A, 1 (7.7%) hyper CVAD B] [p=0.005]. However, no superior CLABSI risk between protocols was found: SWOG vs 7+3 [RR 1.500,95% IC, 0.307 to 6.197], SWOG vs hyper CVAD´s [RR 1.636, 95% IC, 0.301 to 8] and 7+3 vs hyper CVAD´s [RR 3.273, 95% IC, 0.886 to 12].

### 5.1 Hematological recovery and CLABSI risk

An overall of 1393 blood samples were analyzed. A hemoglobin median ≤9 g/dl in all admissions was identified [median 8.17, range 15.7 to 4.4]. Considering hemoglobin at the first admission day, significant differences were found between induction (median 8.45, range 13.8 to 7.3), aplasia support (median 7.75, range 9.1 to 5.3) and CT (median 9.55, range 12.6 to 7.2), p=0.000. The study reported 0.25 thrombocytopenia ratio (thrombocytopenia days related to overall hospital admission days) considering thrombocytopenia (≤20.000 cells/µL) among 541 days. AML patients (median 6, range 33 to 0) revealed superior cumulative thrombocytopenia days (≤20.000 cells/µL) than ALL patients (median 3, range 18 to 0) (p=0.008). Considering CLABSI and non-CLABSI identified, no significant differences between the thrombocytopenia distribution were identified (p=0.736). Considering the number of platelets count ≤20.000 cells/µL at CVC insertion day related to CLABSI, CLABSI risk was not found [RR 2.500, CI 95%, 0.261 to 23.937].

[1] Induction CT
[2] Consodlidation CT

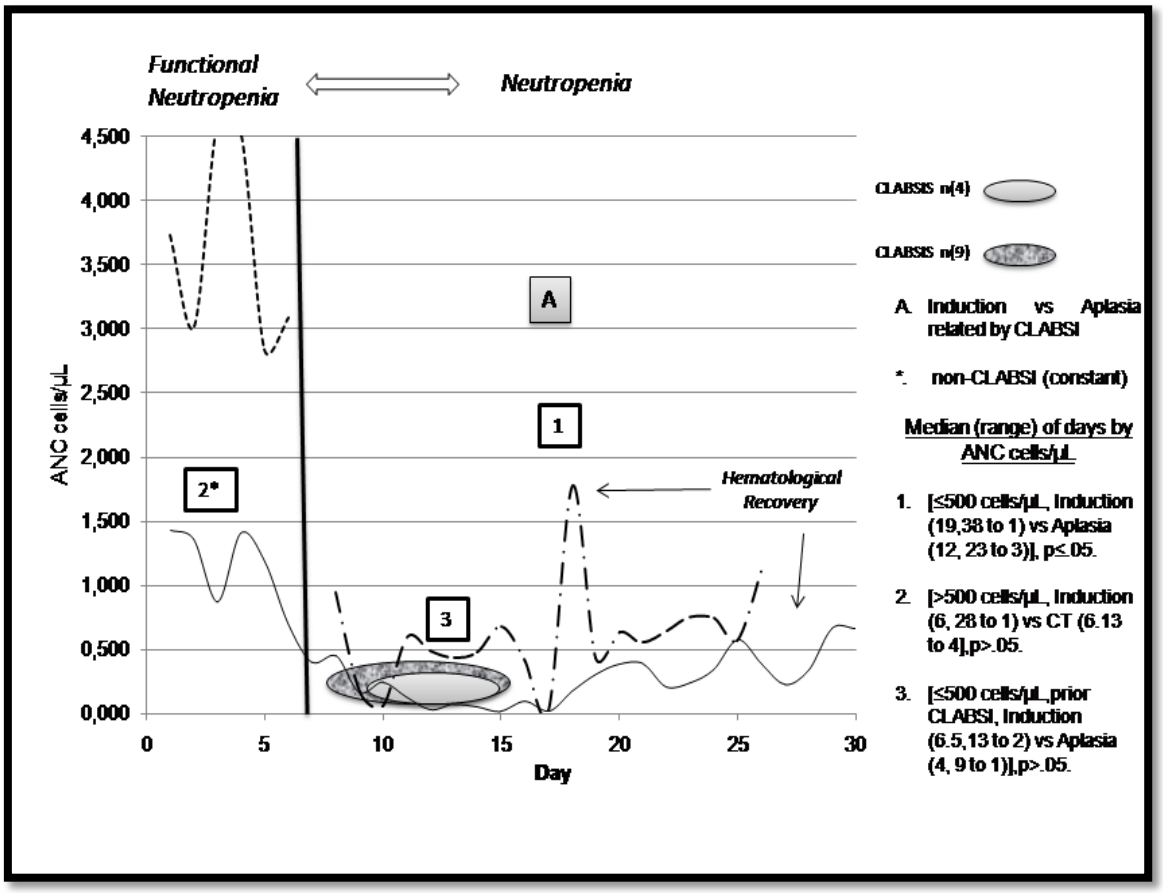
Reporting ANC days (Table V) by hospital admissions phases, no significant CLABSI risk association between induction versus aplasia support was found (RR 0.736, 95% CI, 0.311-1.745). No CLABSI was reported during the CT phase (Figure II).

**Table V. ANC and Hospital Admissions related to CLABSI**

| **ANC by days** (median,range) | **Induction** | **Aplasia Support** | **CT** | **p** |
|---|---|---|---|---|
| ≤ 500 cells/µL | 19(38-1) | 12(23-3) | NA | 0.000 |
| > 500 cells/µL | 6(28-1) | NA | 6(13-4) | 0.323 |
| ≤ 500 cells/µL prior CLABSI | 6.5(13-2) | 4(9-1) | NA | 0.285 |
| ≤ 500 cells/µL CLABSI* | 14.5(30-9) | 12(20-8) | NA | 0.067 |
| ≤ 500 cells/µL non-CLABSI* | 16(26-2) | 13(15-7) | NA | 0.000 |
| > 500 cells/µL non-CLABSI * | 6(28-1) | NA | 6(13-4) | 0.545 |

* Hospital Admissions with CLABSI or non-CLABSI reported

**Figure II. CLABSI and ANC related by Hospital Admission**



## 5.2 Catheter baseline characteristics and infection risk

In total, 42 Hickman catheters (median 1; range 4 to 1 by patient) were inserted, concerning 2130 hospital admission days (ID) including 2007 catheter days. On admission, the CVC was placed in ≤7 days in 90.5% events (median 1, range 17 to 1). No CLABSI was observed in CVC placed after >7 days of admission. CVC was placed in right Subclavian vein in 36 (85.7%) events. No statistical significances were found regarding CVC laterality and CLABSI (p=0.463). Considering ANC at the moment of CVC insertion, CLABSI risk was not found between neutropenia and non-neutropenia patients [RR 1.091, CI 95%, 0.989 to 1.204]. The CVC was removed in bacteriemia cases. (n=5;11.9%), insertion site infection (n= 4;9.5%) and after patient death (n=1; 2.4%); the remaining 32 CVC were removed at the end of treatment (76.2% cases). Twelve CVCs had more than 100 days-life (median 67, range 188 to 8). No admission in the intensive care unit related to CLABSI was reported during the study period.

Local infection signs in the CVC exit - site were reported at least in one day in 26 (46.9%) cases [induction 15 (53.6%), aplasia support 7 (25%), CT 4 (14.3%) and CT + aplasia support 2 (7.1%)]. Considering admissions related to neutropenia, the risk of exit-site infection were higher in induction and aplasia support [RR 3.392, CI 95%, 1.407 to 9.040] than in CT. When CLABSI was considered, local infection signs were reported in 2 (22.2%) cases without microorganism recovered after microbiology local scrub analyses.

Considering total parenteral nutrition (TPN) and CLABSI reports, in 7 (4.5%) hospital admissions TPN was reported. In CLABSI cases identified, no TPN was administrated in the least 72 hours previous to the event. In hospital admissions related to BCs episode, TPN was used in 6 (85.71%) cases.

## 5.3 Transfusion support and CLABSI

An overall of 595 transfusions were reported (Table VI). A median of 2 transfusions (range 30 to 0) was performed by admission episode. Superior number of transfusion support was identified when CLABSI was reported at hospital admission (p=0.011). When CLABSI was reported, only 1 (7.7%) BCs was performed at transfusion support time. In 9 (69.3%) cases, transfusion support was reported between 24/72-hour period prior CLABSI. Other 3 (29%) cases were observed ≥72-hours after transfusion support. A median of 3 admission days prior to first transfusion support (range 27 to 1) were identified.

**Table VI. Transfusion support related by diagnosis**

| | AML | ALL | p |
|---|---|---|---|
| Overall n[median(range)]* | 438[4(30-0)] | 157[1(22-0)] | 0.011 |
| Induction* | 230[8(30-0)] | 73[5(22-1)] | 0.356 |
| Aplasia Support* | 170[5(11-0)] | 65[4(8-1)] | 0.274 |
| CT* | 18[0(3-0)] | 16[0(5-0)] | 0.397 |
| CT+ Aplasia Support* | 20[6(11-3)] | 3[3(3-3)] | 0.500 |

## 5.4 Catheter-related occlusions

A total number of 16 occlusion days (median 1, range 5 to 1) among 10 occlusion events were observed (Table VII). Partial occlusion was identified 8 (80%) times (median 1, range 2 to 1), being complete occlusion reported 2 (20%) times (median 3.5, range 5 to 2). Considering platelet count at the occlusion day, no significant differences were found between partial (median 26.5, range 306 to 7) and complete (median 155.5, range 168 to 143) occlusions (p=0.400). Whereas placement CVC day, a median of 67.5 (range 172 to 17) days to the occlusion was reported. Considering the hospital admission days related occlusion, earlier occlusion events (≤72-hour) after first admission day was observed more frequently than late occlusion events (>72h-hour; median 3, range 27 to 0) [p=0.010]. When occlusion events were identified in induction, its occurred in hospital admission superior to 15 days [RR 3.000, CI 95%, 0.914 to 3.000]. No occlusion after transfusion support or 72-hour after/before CLABSI were observed. Complete occlusions were always identified in non-thrombocitopenic patients, being partial occlusion reported in 2 (25%) cases undergoing thrombocytopenia. No catheter-related thromboses were reported. Overall 4.98 catheter-related occlusion rates per 1000 catheter-days, including partial 3.98 and complete 0.99, were reported.

**Table VII. Catheter-related occlusions development**

| Oclussion type | Oclussion days (OD) | 1.0 cvc line OD | 0.6 cvc line OD | Admission day | Platelets Count* | CVC life-days |
|---|---|---|---|---|---|---|
| Complete | 2 | - | 2 | 16 | 168 | 92 |
| Complete | 5 | 5 | - | 0✲ | 143 | 43 |
| Partial | 1 | 1 | 1 | 27 | 306 | 27 |
| Partial | 1 | 1 | 1 | 1 | 247 | 95 |
| Partial | 1 | 1 | 1 | 2 | 23 | 92 |
| Partial | 1 | 1 | 1 | 3 | 7 | 172 |
| Partial | 2 | 2 | - | 17 | 21 | 17 |
| Partial | 1 | - | 1 | 3 | 20 | 100 |
| Partial | 1 | 1 | 1 | 5 | 30 | 18 |
| Partial | 1 | 1 | 1 | 1 | 123 | 41 |

*First occlusion day; Oclussion reported at the moment of the admission□

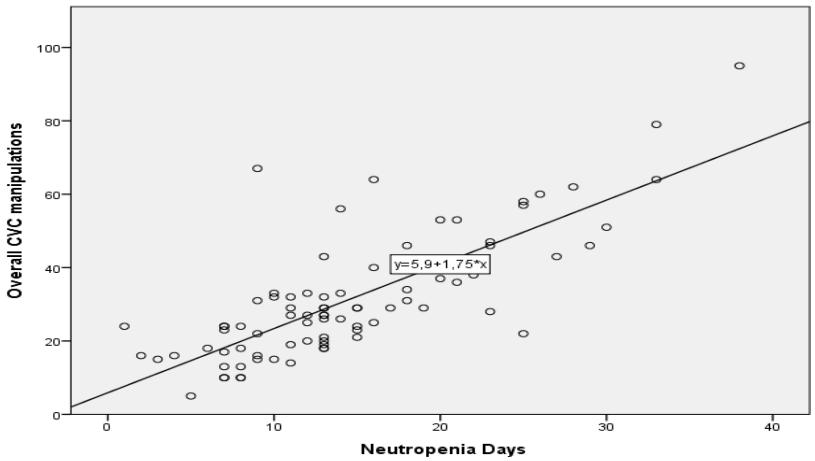
## 5.5 Neutropenia, CVC Manipulations and CLABSI risk

An overall of 1393 blood samples, 595 transfusions, 145 BCs, and 304 CVC-line isolated substitutions were observed. Overall 1212 neutropenia-days were reported. Considering the duration of neutropenia, induction reported superior median of neutropenia-days (median 19, range 38 to 1) than aplasia support (median 12, range 23 to 3) [p=0.000]. When neutropenia-days prior CLABSI was considered, no statistical significance were found between induction (median 6.5, range 13 to 2) and aplasia support (median 4, range 9 to 1), [p=0.285].

A total number of 3032 CVC manipulations by catheter were reported (median 15, range 95 to 3) considering a median of 1 CVC manipulations by day (range, 5 to 0) (Table VIII). CVC-lines were used with perfusion iv (at least one day) in 142 hospital admissions, being only used for blood samples and transfusion support in 12 aplasia support admissions without CLABSI reported.

CLABSI was always reported in neutropenia admissions within cases presenting a median number of CVC manipulations superior to 15. The number of CVC manipulations increases concerning cumulative neutropenia days [r=0.752, p=0.000 with a $R^2$ = 0.605]; non-neutropenia days [r=0.051, p=0.564 with a $R^2$ = 0.004]. (Figure III)

**Figure III: CVC manipulations correlated to neutropenia days**




Taking neutropenia condition into account, CLABSI risk is increased considering CVC manipulations [CLABSI group, mean ±SD, 27.89±3.199; non-CLABSI group, mean±SD, 20.82±1.189; p=0.046] (Figure IV).

**Figure IV : Overall CVC manipulations related to CLABSI in neutropenia**

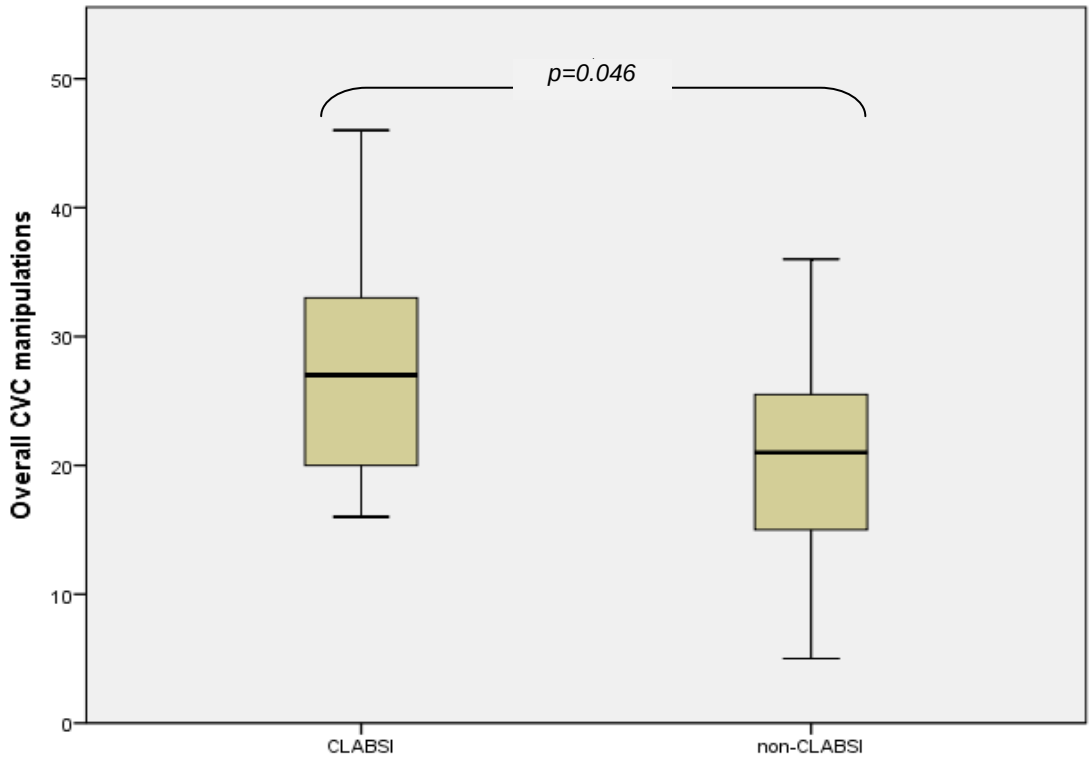



**Table VIII. CVC manipulations ANC related by admission**

| | Induction | Aplasia Support | CT | p |
|---|---|---|---|---|
| **ANC ≤ 500 cells(median,range)*** | 33.5(77-1) | 18(38-4) | NA | 0.000 |
| **ANC > 500 cells*** | 5(23-1) | NA | 5(19-3) | 0.095 |
| **ANC ≤ 500 cells/µL,prior CLABSI*** | 10(12-2) | 7(15-2) | NA | 0.546 |
| **ANC ≤ 500 cells/µL,CLABSI*¥** | 37.5(51-21) | 20(38-14) | NA | 0.067 |
| **ANC ≤ 500 cells/µL,non-CLABSI*¥** | 33.5(77-1) | 13(24-4) | NA | 0.000 |
| **ANC > 500 cells/µL,non-CLABSI*¥** | 5(23-1) | NA | 5(19-3) | 0.147 |

NA not applicable; ¥ Hospital Admissions with CLABSI or non-CLABSI reported

Considering the induction phase as reference, manipulation ratio (median of manipulations by admission; induction=1, aplasia support=0.45, CT=0.12) was reported. No statistical significances were found between the number of CVC manipulations in neutropenic days prior CLABSI in both induction (median 10, range 12 to 2) and aplasia

support (median 7, range 15 to 2), p=0.762. Also no significant CLABSI risk association between induction and aplasia support was found (RR 0.736, 95% CI, 0.311–1.745).

### 5.6 Blood Cultures and Microbiological Recovery

BCs were collected at 48.7% (median 0, range 6 to 0) of all hospital admissions, being positive in 21 (10.4%) reports. No CLABSI was identified after first positivity result; after first negative result, 2 (9.5%) positive BCs were reported. No positive BCs were reported after three negative results. Considering the cumulative days prior BCs assoictaed with ANC by hospital admissions and BCs related by ANC (Table IX), no positive BCs were reported by ANC>500 cells/µL in AML patients, and only 1 (4.7%) positive BC was reported by ANC>500 cells/µL in ALL patients.

**Table IX. Cumulative days prior Blood Cultures related to ANC by hospital admissions.**

| Days | Induction | Aplasia Support | CT | p |
|---|---|---|---|---|
| ANC ≤ 500 cells/µL (median,range)* | 5(19-1) | 4(9-1) | NA | 0.356 |
| ANC > 500 cells/µL * | 4(6-3) | NA | 2(8-1) | 0.254 |

BCs were summarized by hospital admission phases: induction [median 2, range 6 to 0], aplasia support [median 1, range 3 to 0] and CT [median 0, range 1 to 0]. Considering the number of BCs related to CLABSI by hospital admission phases, BCs have been always negative in non-neutropenia induction phases when at least one BCs episode was reported. None CLABSI was observed over three BCs collection in all hospital admissions. (Table X) Fifty-five (%) CT admissions did not report BCs episode. BCs collection risk was superior in induction phase than in aplasia support [RR 1.624, CI 95%, 1.095 to 1.362]. Comparing aplasia and CT, superior risk of BCs collection was reported in aplasia support [RR 4.952, CI 95%, 2.849 to 9.103]. Superior BCs collection risk was observed when neutropenia was reported [RR 5.688, CI 95%, 3.419 to 10.245].

Considering BCs results related to ANC at the moment of the sample, no superior risk to positive reports were found among neutropenia and non-neutropenia population [RR 4.375, CI 95%, 0.715 to 82.238].

**Table X. Blood Cultures results related to episodes and ANC**

| | AML | ALL | p |
|---|---|---|---|
| Blood Cultures, n[median(range)] | 105[1(6-0)] | 40[0(6-0)] | 0.066 |
| Positive | 14[0(2-0)] | 7[0(3-0)] | 0.623 |
| Negative | 91[1(5-0)] | 33[1(6-0)] | 0.451 |
| Positive ANC ≤ 500 cells/µL | 14[0(2-0)] | 6[0(3-0)] | 0.805 |
| Positive ANC >500 cells/µL | 0 | 1[0(1-0)] | 0.121 |
| Negative ANC ≤500 cells/µL | 76[1(5-0)] | 23[1(6-0)] | 0.054 |
| Negative ANC >500 cells/µL | 14[0(3-0)] | 10[0(1-0)] | 0.181 |
| First episode | 92[2(3-1)] | 39[1(6-1)] | 0.815 |
| Positive | 14[0(1-0)] | 7[0(1-0)] | 0.421 |
| Negative | 78[1(3-0)] | 32[1(6-0)] | 0.723 |
| Second episode | 11[0(2-0)] | 1[0(1-0)] | 0.112 |
| Positive | 0 | 0 | NA |
| Negative | 11[1(2-1)] | 1[1(1-1)] | 0.909 |
| Third episode | 2[0(1-0)] | 0 | NA |
| Positive | 0 | 0 | NA |
| Negative | 1(1-1) | 0 | NA |

Febrile resolution (≤72-hours) was observed in 119 (82.1%) first BCs episode, been reported in 12 (92.3%) cases when CLABSI identified. No positive BCs were identified in second and third episode and no fourth BC episode was observed. There were 8 cases (10.7%) when there was a previous antibiotherapy administration before the first BC sample; in these cases no CLABSI was reported. Considering the number of BCs with febrile resolution (≤72- hours) undergoing neutropenia, no significant differences were found between AML [n (71), median 1, range 2 to 0] and ALL [n (27), median 1, range 3 to 0) (p=0.449) patients. In the particular case of a number of BCs with febrile resolution (>72-hours) undergoing neutropenia, statistical significance was observed between patients diagnosed with AML [n (20), median 0, range 1 to 0] and ALL [n (3), median 0, range 2 to 0) (p=0.015). Considering the number of BCs with febrile resolution (>72-hours) undergoing non-neutropenia, in all cases [3 (2.1%)], rate of ANC decline was reported.

Considering CVC-lines microorganism recovery, 1.0 mm CVC-line was positive in 12 (92.3%) cases when CLABSI reported. When colonization is reported,0.6 mm CVC-line was always positive 5 (100%). At least one CVC line (1.0 mm or 0.6 mm) was negative in 5 (31.25%) cases when CLABSI was reported.

BCs results were summarized by CLABSI, microorganism recovered, and symptomatology prior BCs (Table XI).

**Table XI. Microbiological Blood Cultures results and Symptomatology related**

| Source | Gram - | Gram + | Symptomatology ≤72h prior BCs* |
|---|---|---|---|
| **CLABSI**[α] | - | S.Aureus<br>S.Mitis | Hypotension and Respiratory Distress |
| **CLABSI** | - | S.Mitis | - |
| **CLABSI** | K.Pneumoniae | - | - |
| **CLABSI** | Serratia Marcescens | S.Epidermidis | - |
| **CLABSI** | E.Coli | | Chills |
| **CLABSI** | - | S.Aureus | - |
| **CLABSI** | E.Coli | - | Constipation |
| **CLABSI** | E.Coli | - | Constipation |
| **CLABSI** | P.Aeruginosa | - | Chills |
| **CLABSI** | E.Coli | - | Hypotension Headaches, Nausea and Vomiting |
| **CLABSI** | P.Aeruginosa | - | Chills |
| **CLABSI** | K.Pneumoniae | - | Chills |
| **CLABSI** | K.Pneumoniae | - | Chills |
| **Colonization** | P. Aeruginosa | - | Abdominal Pain and Headaches |
| **Colonization** | K.Pneumoniae | - | Chills |
| **Colonization** | K.Pneumoniae | - | - |
| **Colonization** | - | S. Salivarius | - |
| **Colonization** | K.Pneumoniae | - | - |
| **Secondary BSI** | E. Coli | - | Mucositis and Diarrhea |
| **Secondary BSI** | E. Coli | - | Abdominal Pain, Mucositis and Diarrhea |
| **Secondary BSI** | P. Aeruginosa | - | Chills |

*Fever associated; non-MBIm (S); [α] CRBSI

The only gram-negative bacteria reported by ALL patients were Klebsiella Pneumoniae, being the remaininggram-negative bacteria associated with AML patients. E.coli (n=4; 30.7%) was the most representative microorganism identified in CLABSI events, being the

Klebsiella Pneumoniae (n=3;60%) the most representative microorganism linked to CVC colonization events. No previous colonization reports to CLABSI were observed.

The study suggested an overall 0.80 MBIm ratio associated with colonization events. No fungus species was identified. (Table XII) Overall, CRBSI and CLABSI rates per 1000 catheter-days were reported as 0.49 [AML 0 and ALL 1.63) and 6.47 [AML 6.45 and ALL 6.52], considering overall 0.63 MBIm ratio associated [AML 0.62 and ALL 0.69].

**Table XII. Microorganism recovery: CLABSI, Colonization and MBIm related**

| **Microorganism Recovered, n(%)** | **AL (overall)** | **AML** | **ALL** |
|---|---|---|---|
| **Gram +** | | | |
| **CLABSI** | **6** | **4(66.7)** | **2(33.3)** |
| **MBI** | **2(40)** | **1(33.3)** | **1(50)** |
| Streptococcus Mitis | 2(100) | 1(100) | 1(100) |
| Streptococcus Salivarius | - | - | - |
| **Others** | **3(60)** | **2(33.3)** | **1(50)** |
| Staphylococcus Aureus | 2(66.7) | 1(50) | 1(100) |
| Staphylococcus Epidermidis | 1(33.3) | 1(50) | - |
| **Colonization** | **2** | **1(50)** | **1(50)** |
| **MBI** | **2(100)** | **1(100)** | **1(100)** |
| Streptococcus Mitis | 1(50) | **-** | 1(100) |
| Streptococcus Salivarius | 1(50) | 1(100) | - |
| **Others** | - | - | - |
| Staphylococcus Aureus | - | - | - |
| Staphylococcus Epidermidis | - | - | - |
| **Gram –** | | | |
| **CLABSI** | **10** | **7(70)** | **3(30)** |
| **MBI** | **8(80)** | **5(71.44)** | **3(100)** |
| Escherichia Coli | 4(50) | 4(80) | - |
| Klebsiella Pneumoniae | 3(37.5) | - | 3(100) |
| Serratia Marcescens | 1(12.5) | 1(20) | - |
| **Others** | **2(20)** | **2(28.6)** | - |
| Pseudomonas Aeruginosa | 2(100) | 2(100) | - |
| **Colonization** | **4** | **1(25)** | **3(75)** |
| **MBI** | **3(75)** | - | **3(100)** |
| Escherichia Coli | - | - | - |
| Klebsiella Pneumoniae | 3(100) | - | 3(100) |
| Serratia Marcescens | - | - | - |
| **Others** | **1(25)** | **1(100)** | - |
| Pseudomonas Aeruginosa | 1(100) | 1(100) | - |

## 6. Discussion

AL patients are considered a special population due to the higher number of hospital admissions and the difficulty to access catheter-related complications across time. Clinical research, CVC-related, in AL patients undergoing high dose CT is infrequent, probably due to the low incidence of the disease and to the difficulty to find an appropriate population sample [7, 29]. Studies regarding AL that are only based on the number of patients could and should be considered a bias due to the fact that multiple hospital admissions of these patients that lead to a different statistical distribution. Indeed, this study revealed no statistical differences between AL diagnoses associated with the number of patients, and the diagnose distribution was superior in AML patients related to hospital admissions phases (induction, aplasia support and CT).

CLABSI could be considered a rare event in non-neutropenic patients; in consequence AL patients seem to be an optimal CLABSI research population considering neutropenia ratios reports and CVC use. Taking this into account, aplasia support should be included in clinical studies, being mostly focused on induction reports. [28]

Infection risk and CLABSI in AL patient

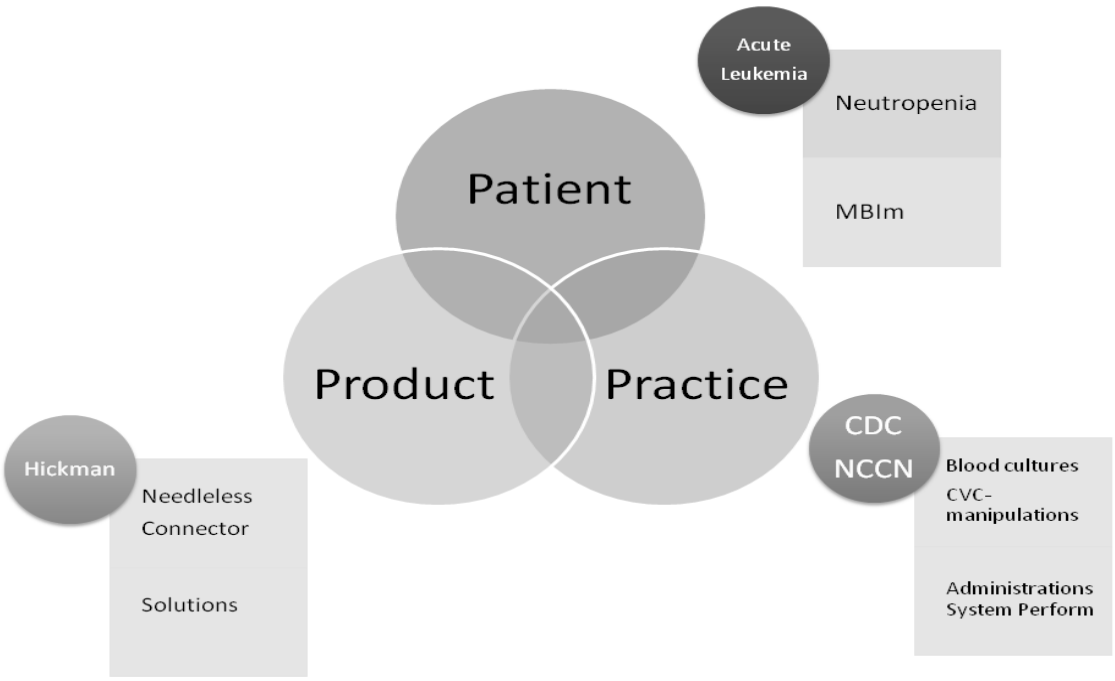
Considering the CLABSI definition and the fever as non-specific sign of infection, when a BC collection is negative the infection source is considered unknown. AL patients reported BCs collection in induction, aplasia support and CTs phases, being BCs risk superior in hospital admissions related to neutropenia. The duration of neutropenia could improve a superior number of CLABSI events in induction, reporting superior duration of neutropenia that aplasia support. Even considering a superior duration of neutropenia associated with induction, no significant statistical differences was found between the CLABSI risk and cumulative neutropenia-days previous to CLABSI among induction and aplasia support phases. Being neutropenia ratio and negative ANC ≤500 cells/µL BCs results tendency superiors in AML patients, a higher infection risk could be considered in this group. However, AML and ALL patients did not report significant statistical CLABSI risk differences, in consequence, induction and aplasia support (concerning AML and ALL patients) could be considered similar hospital admissions CLABSI associated with neutropenia .

HAST, CLABSI rates and CVC management

Studies indicate that the CVC is an indispensable tool in these patients. [26] Blood samples, transfusion support and BCs collection could be considered the most representative causes of CVC manipulations, mostly in induction and aplasia support. In patients undergoing CT consolidation fewer CVC manipulations were observed.

Several organizations used CLABSI surveillance programs to assess infections associated with CVC insertion and maintenance procedures. Surveillance data can provide information needed to improve patient outcomes and the quality of patient care. CLABSI rate reports are based in diferent departments data (ICU, hematology-oncology, blood marrow transplant, acute leukemia units…) in both adult and pediatric populations. [27] In the particular case of hematology-oncology departments, a low number of hospital admissions can be associated with the multidisciplinarity of these units that include also patients with solid tumors [67], influencing infection rates. Even considering CLABSI assessment related by pathology, in several cases CLABSI rates could not be associated with a specific central-line device, being CVC management details not reported in mostly cases [29, 30]. These findings can be the basis of a high frequency of low level CVC guideline recommendations. Being HAST framework based on patient, practice and product variables this could be considered a good tool associated with effectiveness of clinical research (Figure V).

**Figure V. Patient, Product and Practice related to Acute Leukemia Patients**



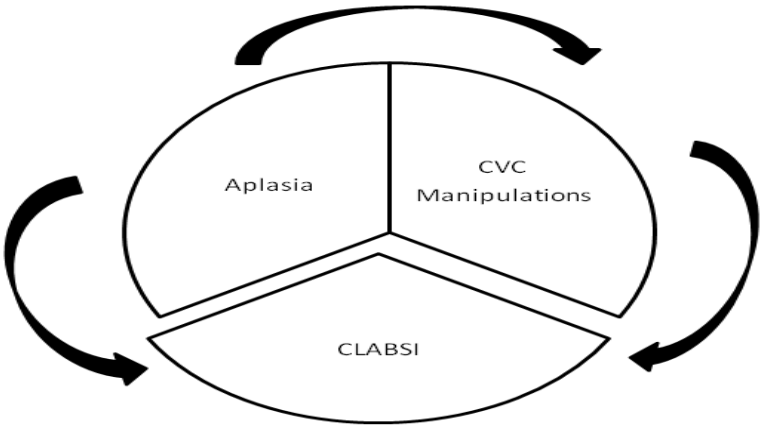
This study indicated neutropenia as the most important variable related to adult AL patient. Biofilm formation [21,22] could be associated with patient, product and practice variables and it is considered a modifiable risk factor concerning CRBSI rates. [13]

CVC management procedures as blood samples drawn at the moment of CVC-line change, CVC-line maintenance every 72-hours (changing needleless connectors and administration sets), administration sets removed in BCs episodes, optimal choice of needleless connectors used (positive pressure mechanical valves are associated to high infection rates) [13,19-20], turbulent flush and positive-pressure locking techniques, could reduce unnecessary CVC manipulations and influence CLABSI and CRBSI reports. [11] Besides that, some CVC procedures (changing needleless connectors and administration sets in all BCs episodes) are used in the attempt to improve product colonization risk reduction and could be on the basis of high frequency of febrile episode resolution in 72-hour period reported. For example, if a needleless connector was colonized, changing this product as previously referred could remove the possible infection source. Besides, some of these practices could influence the low number of second BC episodes and CRBSI rates reported.

Neutropenia and CVC manipulations related to CLABSI risk

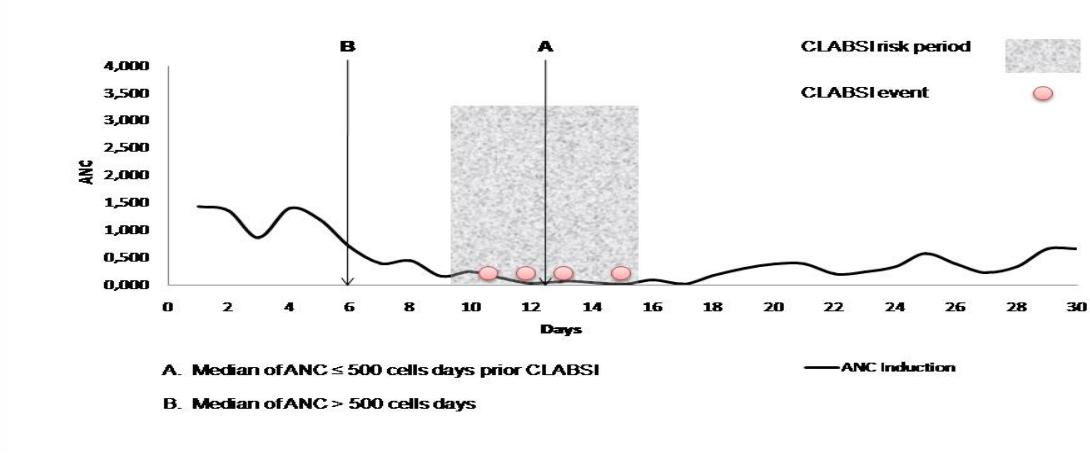
Neutropenia is considered a major CLABSI risk factor [12]. This study suggested that aplasia (neutropenia, anemia, and thrombocytopenia) increases the number of CVC manipulations (Figure VI), mostly due to several blood samples, transfusion support and BCs collection. [9-19]. This study reported a manipulation ratio higher in induction than in aplasia support and CT. However, similar CLABSI rates were reported between induction and aplasia, being a CLABSI considered a rare event in CT. This could be explained considering that cumulative neutropenia days increases the number of CVC manipulations. This fact associated to neutropenia increases CLABSI risk. In consequence, this study suggests that neutropenia and CVC manipulations association are major CLABSI risk factors. Therefore, when appropriated CVC management, isolated or cumulative CVC manipulations in non-neutropenia could be considered minor CLABSI risk factors.

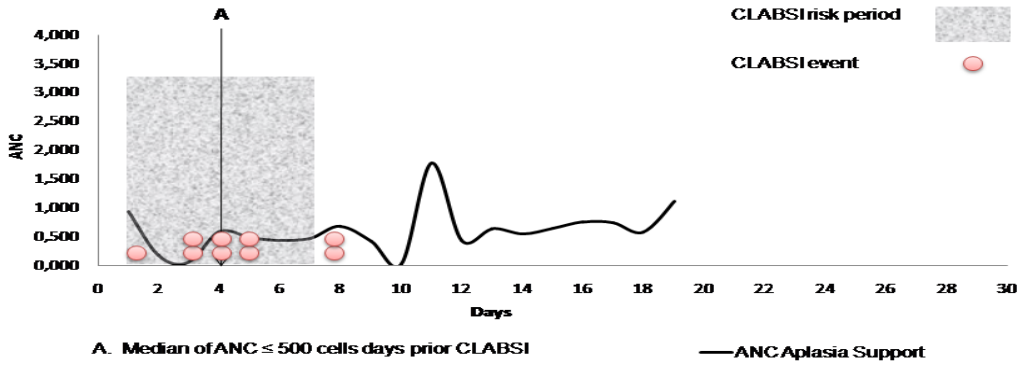
**Figure VI. Aplasia, CVC manipulations and CLABSI**




Considering neutropenia-days prior to CLABSI and biofilm formation risk period (48/72-hour period) [15], risk phase is higher between days 9 to 15 in induction and days 1 to 7 in aplasia support. (Figure VII)

**Figure VII. CLABSI risk period related to neutropenia hospital admissions**



CVC management and occlusions among hospital admissions

This study reported an higher number of transfusion support and blood samples in induction, CT, and higher frequency in aplasia support admissions. When nurse-to-patient ratio is poor [29], the transfusion support procedure management could be affected due to the elapsed time between transfusion support ending and infusion resume or transfusion withdrawal. If nurse-to-patient ratio is modified, quality of CVC-care considering catheter-related occlusions and CLABSI/CRBSI rates should be considered. This study did not report catheter-related occlusions associated with transfusion support and it could be considered a good quality CVC-management indicator.

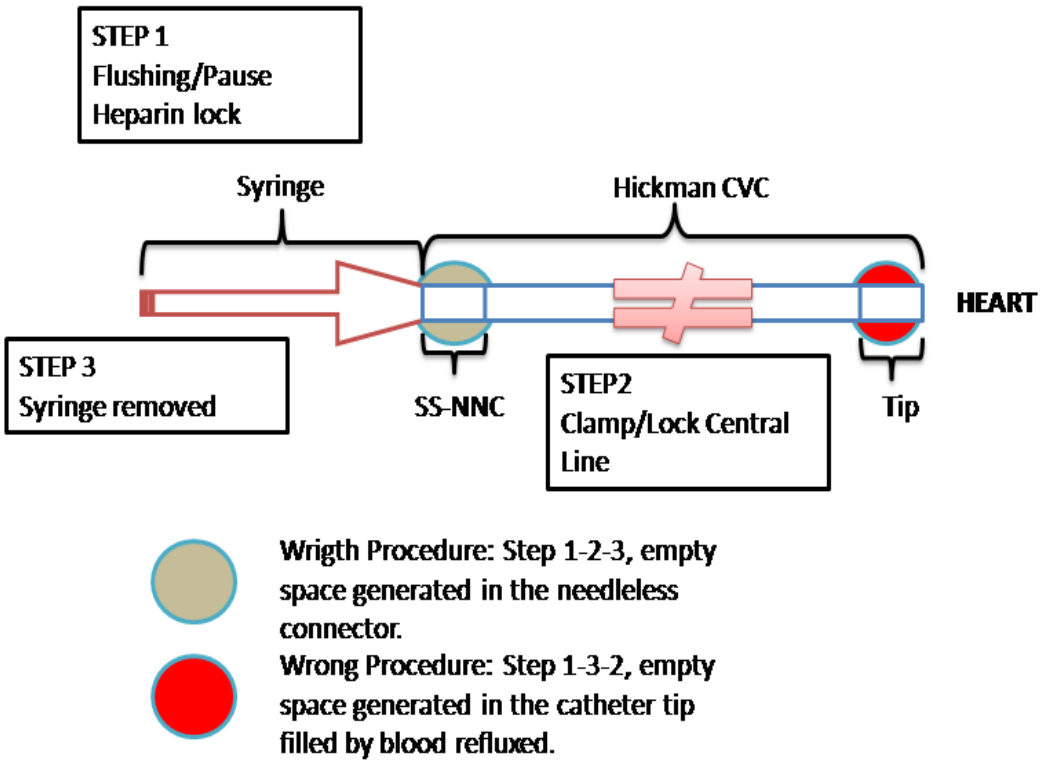
Catheter-related occlusion and infection should not be dissociated. [7, 34, 52] An adequate clean sweep of the catheter-lumen using sodium chloride 0.9% through push-pause technique seems to be essential to secure CVC pattency and reduce biofilm formation risk. [31, 45, 54-56] This study reports the use of heparin to CVC-lock after catheter-lumen clean sweep. Considering heparin short-life, low heparin concentration (20-30 UI) and non-bleeding reports, the use of heparin to CVC-lock could be considered of dismal risk. In this study we indicate that heparin could reduce cumulative fibrin deposition (possible biofilm and thrombi formation source) [21, 22, 40, 60] in the first hours after CVC manipulation based on the CRBSI and catheter-related occlusion rates reported. Considering that, the relationship between heparin and catheter-related infections should be studied. [31,45,59]

In the last decade the MVC-PP replaced SSNC to reduce the use of heparin and catheter-related occlusions. [67] The design of an MVC-PP versus SSNC showed an important structural difference between them: the MVC-PP allows the fluids to enter and return inside the connector through the internal valve; on the other side the SSNC allows the fluids to enter and return inside the connector without resistance. Flushing CVC above 0.1 ml is enough to create positive pressure in MVC-PP and if just a little more product is infused it is expelled. Even using heparin CVC-locks, biofilm formation risk related to cumulative fibrin deposition through the internal valve seems to be on the basis of superior infection rates associated with MVC-PP. [26] Using SSNC, CVC-line clamp before connector syringe withdrawal could be considered a positive-pressure technique. (Figure VIII)

When the syringe is removed, empty space generated inside the connector is created. It does not allow the blood reflux into the catheter tip, and consequently the probability of occlusion by small thrombi formation is reduced. In the particular case of partial occlusions reported, the study reported the resolution of all events in less of 48-hours. In

consequence, this study suggested that the use of heparin to CVC-lock could help to reduce and resolve partial occlusions.

**Figure VIII. CVC-line clamp positive-pressure technique**




Catheter-related occlusions were usually reported in the literature in second and third week after CVC-placement. [51] This study reported only two partial occlusions considering ≤30 days CVC-placement. Besides, this study suggested that catheter-related occlusion risk was not associated with platelet count; so CVC-management could be considered a major catheter-related occlusion risk factor versus CVC-placement time and platelet count at the occlusion-day.

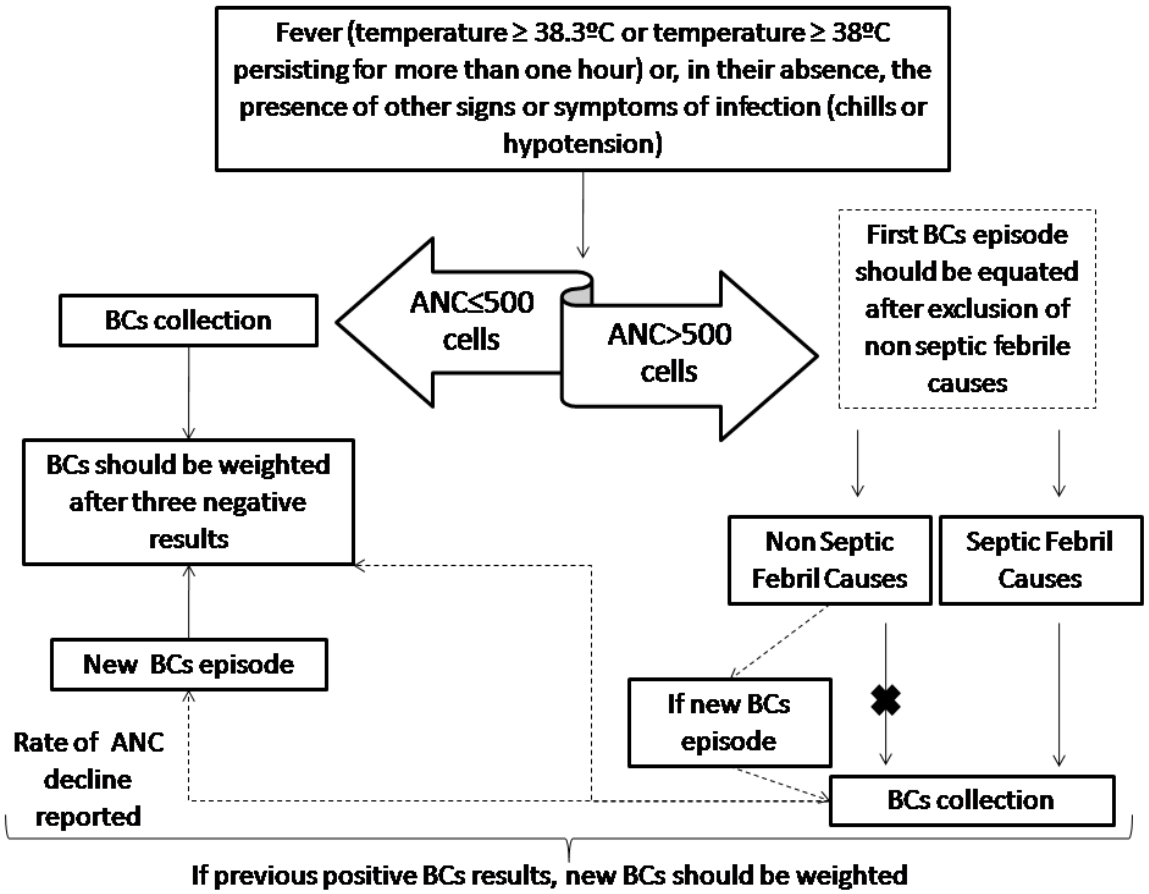
Blood Cultures Collection protocols, sets and CLABSI

Concerning biofilm formation risk, BCs should be collected every 72-hour period until symptomatic recovery. However, considering our BCs episode results and if not clinically indicated, BCs should be only obtained until second episodes; and when positive BCs are identified; the new BCs collection should be weightened.

Taking BCs episode risk, undergoing hospital admissions and neutropenia into account, BCs should be always obtained in patients undergoing neutropenia (induction and aplasia support). However, considering the positive BCs results tendency (it is not ANC related and CLABSI is always reported undergoing neutropenia) and the maximum of one BCs episode related to CT phases, the first BCs collection undergoing non-neutropenia (induction and CT) should be weightened.

Considering BCs obtained undergoing non-neutropenia and febrile resolution trending, the need of BCs collection in the first febrile episode should be equated after exclusion of non septic febrile causes (as drugs and transfusion related side effects) leaving the sample collection for a second event. Considering negativity trending after second negative results, the only new BCs episode should be considered clinically indicated. Several doubts concerning the number of culture specimens set when obtaining BCs were considered. The NCCN recommends obtaining one peripheral venipunctures and one catheter culture for distinguishing between CRBSI and BSI. [10] Considering this recommendation, a false CLABSI negative could be identified in one third of CLABSI reported in this study, if BCs had been collected from one of CVC-lines and it was negative reported and positive peripheral vein, BSI had been reported in place of CLABSI in these cases. (Figure IX)

**Figure IX. Blood Cultures Protocol in AL patients ANC related**




CLABSI rates to zero [9] and MBIm. Is it possible in AL patients naturally link this to neutropenia?

Colonization through mucosal disruption and epithelial loss could be on the basis of CLABSI. [12-15] This study reported a high rate of MBIm (*Viridians group, Streptococci and Enterobacteriaceae*). When examining MBIm with CLABSI rates assessment by HAST insight [7], the impact of CVC management procedures remains unknown. [10] The study suggested a similar MBIm ratio among AL patients considering the same practice and device used. MBIm recovery seems to be related to neutropenia when CLABSI reported, especially with the cumulative neutropenia-days, being not associated with the duration of neutropenia itself. However, the CVC manipulations could be on the basis of the MBIm related to CLABSI, too[10]. Considering that, several difficulties to understand the colonization source, patient or healthcare professional, are revealed.

The relationship between MBIm and neutropenia could be an appropriate insight to assess the balance between patient and practice related to CLABSI. In fact, CLABSI rates

associated with high MBIm ratios undergoing neutropenia could be considered a good infection control indicator related to CVC management. Considering the dichotomy associated with the possible infection source, MBIm assessment should not be dissociated from CLABSI, being zero CLABSI rates a difficult aim to achieve in infection control programs, in these patients.

## 6.1 Scope and limitations

The clinical research related to neutropenia and CVC management in AL patients is scarce. The most important advantage of our study is that it was performed in a specific immunocompromised population with an accurate department infection control description and in a homogeneous sample. This is a retrospective study and a lack of documentation could be possible. However, our electronic medical record reports a systematic description of CVC procedures by nurse team. Multicenter studies are needed to increase the population study, however, due to a medley of clinical research in hematology-oncology patients related to CVC management procedures, is possible to find two departments following the same guideline recommendations without reports of different CVC procedures (e.g., mechanical valve needleless connectors or split septum connectors, heparin or sodium chloride to CVC lock). Besides, it could be considered an infection control assessment bias. Considering AL and CLABSI rare events, single-center prospective cohort studies should not be performed due to high risk of department changes across the years (bias). Prospective studies with a multicenter larger size and several homogenic management CVC procedure descriptions should be performed to increase the sample and assess these findings.

## 7. Conclusion

The study concludes that:

- In neutropenic patients, undergoing induction therapy or in aplasia support, CLABSI risk increases along with cumulative neutropenia days prior CLABSI and CVC manipulations.
- MBIm ratio should be included to CLABSI rates assessment.
- Patient, product and practice should be considered to effectiveness of CVC clinical research.

The study suggests that:

- ✓ Different protocols concerning BCs collection related to ANC should be considered.
- ✓ BCs should be obtained in a peripheral vein and both CVC-lines to prevent false negative results.
- ✓ The relationship between heparin and catheter-related infections should be studied.
- ✓ Catheter-related occlusion risk is not related to platelet count, being the CVC-management considered a major catheter-related occlusion risk factor.

Future Perspectives

The successful reduction of CVC complications is related to the quality of its care. The CVC is a sterilized product, being infected by the patient, professional or environment. Future high-quality CVC management descriptions considering patient, product and practice, could help to increase the infection control knowledge. Taking infection risk class and manipulation ratio prevision into account, an appropriate central line device associated with the patient could be considered (midline, PICC, Hickman…). In fact, new tools could be assessed to reduce CVC manipulations. However, several departments around the world reports limited-resources, being the CVC procedure descriptions (ex. positive pressure techniques) a wonderful help to reduce infection rates in these cases. In the particular case of departments with nurse-poor-ratio reduced and related to CLABSI risk increased, nurse staff reinforcement should quickly be considered.

The development of CVC manipulation protocols could help to reduce the infection risk associated. It is not only important in patients with high manipulation ratio related, in fact,

is possible to find institutions where the CVC is not manipulated in isolated admissions to reduce the infection risk, being blood samples collected in a peripheral vein. If the patient has a CVC line, blood samples should not be collected from a peripheral vein to reduce the number of CVC manipulations. Protocols of CVC manipulations concerning performance and cumulative number should be implemented.

BCs protocol development could help to reduce unnecessary BCs collection and improve quality of life to these patients.

Considering the MBIm, microbiological studies should be developed to find the source of the colonization (appendix III). If the patient is considered the source, intervention programs considering mouthwashes and special nutrition should be implemented. If the professional is considered the source, education program (considering theoretical and practical insight) seems to be the best option.

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# APPENDIX I

IPOPORTO
INSTITUTO PORTUGUÊS DE ONCOLOGIA DO PORTO FG, EPE

Parecer CES IPO: 137/2016
Assunto: Pedido de realização de um projeto de investigação intitulado ***"Central-line associated bloodstream infection rates and blood cultures collection assessment in Acute Leukemia inpatients: retrospective cohort study".***
Investigador: **Enf. José Martinez**
Data: 16 de junho de 2016

**PARECER**

**É parecer desta CES, não existir impedimento de natureza ética ao desenvolvimento do referido estudo de Investigação.**

Dr. Artur Lima Bastos
Presidente da CES – IPO Porto EPE

RUA DR. ANTÓNIO BERNARDINO DE ALMEIDA
4200-072 PORTO - PORTUGAL
T (+351) 22 508 40 00 E-MAIL:
F (+351) 22 508 40 01 dinoc@ipoporto.min-saude.pt

Capital Social: 39 900 000,00€ Registado na Conservatória do Registo Comercial do Porto com o Nº 57 884 - NIPC 506 382 299

# APPENDIX II

**Projeto de Investigação Clínica**

*Title: Needleless connector devices: Acute Leukemia patients, CLABSI and Mucosal Barrier Injury Microorganisms insight.*

**Equipa de Investigação**

- ✓ **Investigador Principal:**

Prof. Doutora Ana Espirito Santo

Assistente Hospitalar no Serviço de Onco-Hematologia; Ext 7753

Email: ana.esanto@ipoporto.min-saude.pt

- ✓ **Co-Investigador- Coordenador interno:**

Enfº Jose Manuel Ferrer Martínez

Enfermeiro no Serviço de Onco-Hematologia; Ext 2601

Email: jmmartinez@ipoporto.min-saude.pt

- ✓ **Co-Investigador- Supervisão Investigação:**

Prof. Doutor Rui Medeiros

Coordenador do Grupo Molecular e Patologia viral/Professor Associado; Ext 5414

Email: ruimedei@ipoporto.min-saude.pt

- ✓ **Co-Investigador- Supervisão clínica (Hematologia):**

Dr. JoséMário Mariz

Director do Serviço de Onco-Hematologia; Ext 7645

Email: mariz@ipoporto.min-saude.pt

- ✓ **Co-Investigador- Supervisão clínica (Microbiologia):**

Dr. Filipe Trigo

Assistente Hospitalar Graduado de Patologia Clínica do Serviço de Microbiologia; Ext 5402

Email: afonso.trigo@ipoporto.min-saude.pt

***Needleless connector devices: Acute Leukemia inpatients, CLABSI and Mucosal Barrier Injury Microorganisms insight***

## *1. Introduction*

The purpose of this study is to understand the mucosal barrier injury microorganisms(MBIm) related to Central-line associated bloodstream infections through the assessment of acute leukemia patients using Hickman® Catheter, considering microbiological recovery of needleless connector devices, Blood cultures, and Local CVC insertion site.

Infectious diseases are important causes of morbidity and mortality in hematology oncology patients. Patients with AL, have an higher risk of neutropenia due to high-dose chemotherapy treatments and to malignancy itself.[1-2-3] Multiple chemotherapy cycles, antibiotic resistant bacteria, high transfusion rates are known predisposing factors that increase incidence and prevalence of bloodstream infections (BSI).[4-5-6]

Healthcare and Technology Synergy (HAST) framework considered patient, product and practice as the central elements related by effectiveness of clinical research associated to central venous catheters.[7]Insertion CVC procedure was largely studied and compared with the management CVC procedure. The real value of CVC management still remain unclear due to the low description and few management details reports.[8]

Regarding BSI in patients with central-line devices, CLABSIis considered the classic definition in surveillance programs,being CRBSI (Catheter-related bloodstream infection) the most used definition regarding diagnosis and treatment purposes.[9] Zakhour and colleagues published in *Lancet Infection Diseases* (2016) a review of the Catheter-related infections in patients with haematological malignances suggesting an incidence of 14.4 CLABSI rate per 1000 catheter days.[9]Recently the new conceptof MBIm was added leading to a harder assessment of the management CVC procedures, especially in hematology-oncology departments, where the infection due to MBIm is common.[10]Adjusting CLABSI rates to MBIm events, this value decreases to 8.2 in acute leukemia patients.[9]

The colonization of the intraluminal route from the catheter tubing connection, catheter hub or IV fluids, are considered the most important infection threats.[11] Several studies have identified the biofilm formation by individual multi-resistant pathogens as a principal source of infection.[12-13] The methillin-resistant *S.aureus*, vancomycin-resistant *Enterococcus*, *C.difficile*, extended-spectrum β-lactamase-producing gram-negative bacilli and *Candida* are considered the most important microorganisms that cause nosocomial

infection.[14-15] If colonization progresses and clinical infection occurs, cultures should be obtained and empiric antibiotics started at the time of presentation.[15-16] The management of blood cultures collection in neutropenic patients with fever is not consensual in the literature concerning the number of sets obtained through the catheter and peripheral vein.However,there is no doubt about the importance of collecting microbiological blood from central catheter lines and peripheral vein to determine the source of bloodstream infection based on the differential time to positivity(when samples are collected from CVC lines and become positive 120 minutes or more before samples from peripheral vein, it is known as differential time to positivity).[18].[16-17-18]

Several doubts still remain concerning the real influence of management CVC procedures in the incidence of CLABSIS associated to MBIm.[10] Maria Guembe and colleagues published in *Journal of Clinical and Microbiology*(2015) an original research relating the importance of needleless connector's microbiology assessment to suggest the source of CVC colonization and infection, especially in higher infection risk populations as acute leukemia patients.[19]

## 2. ***Objectives***

a) Identified MBIm in CVC devices associated to CVC management or Patient source;
b) Report a colonization map of the NCs in every internment;
c) Understand the relationship between NC and hub colonization;
d) Improve a new microbiological assessment based on NC cultures;

## 3. ***Hypothesis Test***

The null hypothesis is considered:

$H_o$: MBIm recovered in Blood Cultures collection are not associated to CVC management procedures related to CLABSI.

The alternative hypothesis is considered:

$H_1$: MBIm recovered in Blood Cultures collection are associated to CVC management procedures related to CLABSI.

NCs, BCs, Swipe CVC insertion site microorganism recovered are considered the exposure or event of interest. CLABSI related to management CVC procedures or MBIms are considered the outcomes of interest.

## *4. Material and Methods*

Selection and Description of Participants

A single-center prospective cohort study is performed, including all consecutive AL in patients using a Central Venous Catheter for more than 72h, undergoing chemotherapy treatment (CT)or in aplasia support, since September 2017 to February 2018.

Patients older than 18 years old, with newly diagnosed or relapsed AL, admitted in CT or aplasia support, with CVCs introduced in the study period are included.

Data Collection

Data concerning patient's background is prospective collected. The daily data assessment ends when the CVC is removed by sepsis or end of use. When last patient is eligible to the study a minimum of one month follow up is considered. The baseline demographic data is collected in the placement day of CVC and assessment is encompassed in every hospital admission.

Technical Department Information

Twenty bed units distributed along eight double rooms and four single rooms equipped with positive pressure ventilation and HEPPA filters. Acute Leukemia, non-Hodgkin, Hodgkin Lymphoma and Multiple Myeloma patients are admitted in the department. The insertion of CVCs is performed by medical staff in a proper room, specially equipped for the procedure and only used with this intent[9],located at department and daily management of CVCs is performed by trained nurse staff.

Blood Cultures Collection and Empirical antibiotic use policy

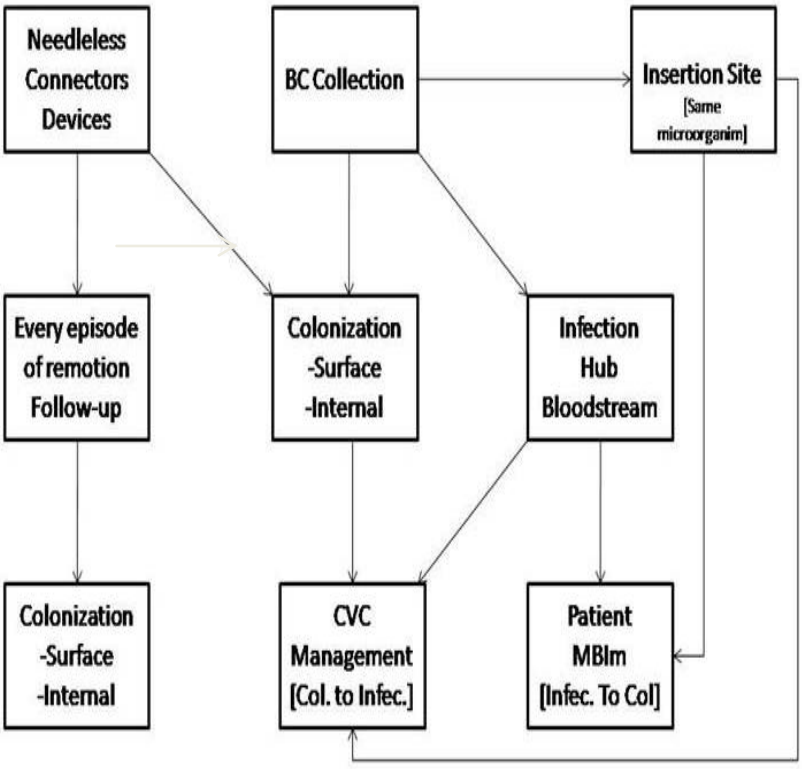
BCs are collected by control indication[16] and non-department and hospital acquired infections are not included in the study. For every episode with indication for BCs, samples are collected first from peripheral vein followed by CVC lines with no more than five minutes between them The BC collection is performed by one nurse. BCs samples are collected (with a minimum of 5ml of blood, when possible) in to BACTED PLUS Aerobic/F® vials[17] and analyzed by the microbiological department. Needleless connector's (NC) devices are removed before BCs collection. When BCs are collected, an insertion site swipe is performed. When negative bloodstream is reported and positive NCs devices are reported, colonization is considered

Large spectrum antibiotherapy is started as the Guidelines for Intravascular Catheter-related Infection of Infectious Diseases Society of America (IDSA, 2009) recommend to

gram-negative bacteria infections in patiens undergoing neutropenia or septicemia special conditions.[20]

Blood Cultures Assessment

All episodes of positive blood cultures are analyzed in all the admissions, and all negative blood cultures are counted to epidemiological research. NC are analyzed and removed every 72h or in every BC episodes. When microbiology results are positive in NC and negative in BC collection (hub and bloodstream), management CVC is considered the source of NC colonization. If NC and BC are positive with the same microorganisms, colonies count between hub and NC determine the source of infection. However if NC and BC collection reports different microorganisms, the patient is considered as infection source. If the insertion site swipe and NC reports positivity with the same microorganism, and BC are negative, management of CVC is considered as colonization CVC source. If BCs are positive with the same microorganism reported in NC and site swipe, CVC management is considered as infection source[21] (Fig 1).




NCs Flowchart (Fig 1)

The assessment of CRBSI or CLABSI is complete by the analysis of the microbiological results by clinical specialist nurse and hematologymedical specialist evaluation. Blood cultures collected by control indication and non-department and hospital acquired infections are not included in the study.

Product and practice management

The management of CVCs followed the CDC (2011) guidelines recommendations.[22] Hickman® catheters (Vygon®), are inserted, without any antimicrobials, in the subclavian vein with double Lumen (CH/F 7, No.1=0.6 and No.2=1.0). No antibiotic prophylaxis is performed. Specific technical information of CVC management includes the use of: chlorhexidine 2% in alcohol 70% solution to needleless connector disinfection [split septum needleless connector (Bionecteur®) (Fig 2) and Octopus®(Fig 3 ). Sodium heparin 20UI/ml (Fibrilin®) is used to CVC lock.

Bionectecur® (Fig 2) Octopus® (Fig 3)

Protection of personal data

These study is attached to the “Central-line associated bloodstream infection rates and blood cultures collection assessment in Acute Leukemia inpatients: retrospective cohort study” thesis approved by the Ethics Committee (CES IPO: 137/2016) of the Portuguese Institute of Oncology (Porto) in 16-June-2016. All data are treated in compliance with the Portuguese Law nº 67/98 of 26 October concerning the protection of personal data.

## *5. Human Resources*

The human resources involve Nurse, Medical and Technics staff of the Oncology-hematology and Microbiology department.

## 6. ***Study Budget***

| | |
|---|---|
| Laboratory :<br>Microbiological cultures of all specimens collected<br>Management of NCs for microbiological cultures | 2500€ |
| Consumables (material and laboratory resources)<br>Estimative of 100 NC devices/month | 4000€ |
| Publications Fees<br>e.g. Journal of Hematology-Oncology | 2000€ |
| Total | 8500€ |

## 7. ***Chronogram***

| Month | Project | Ethics | Data Collection | Data Analysis | Publication |
|---|---|---|---|---|---|
| May | | | | | |
| June | | | | | |
| July | | | | | |
| August | | | | | |
| September | | | | | |
| October | | | | | |
| November | | | | | |
| December | | | | | |
| January 2018 | | | | | |
| February | | | | | |
| March | | | | | |
| April | | | | | |
| May | | | | | |
| June | | | | | |

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